Study design: Male mice received vehicle or the test article once weekly beginning 28 days before cohabitation and continuing through the last week of the 21 day cohabitation period for a total of 8 doses. They were sacrificed at the end of the cohabitation period.

Female mice received the vehicle or test article once weekly beginning 15 days before cohabitation and continuing for one additional dose after confirmation of mating for a total of 3 to 5 doses. The females were sacrificed on GD11.

Cohabitation was for a maximum of 19 days. Females with spermatozoa in a smear of vaginal contents and/or a copulatory plug *in situ* were considered to be at Gestation Day (GD) 0.

Parameters and endpoints evaluated:

Parameters and endpoints evaluated for this study are shown in the table below.

Endpoint	Timing
Observations	2X daily
Body weight	Daily during treatment (M and F) Daily post-treatment (F only)
Clinical chemistry and hematology (~ half of the male mice in each dose group)	At termination
Sperm motility and cauda sperm concentration	At termination (end of cohabitation period)
Organ weight (males only: spleen, thymus, right testis, left testis, left epididymis (whole and cauda), right epididymis, seminal vesicles (with and without fluid) and prostate	At termination (end of cohabitation period)
Bone marrow smears (males only)	At termination (end of cohabitation period)
Caesarean section examination - # and distribution of corpora lutea, implantation sites, and viable and nonviable embryos	At termination (GD11)
Toxicokinetics (~ half of the male mice in each group and all of the female mice)	At termination
Immunogenicity (~ half of the male mice in each group and all of the female mice)	At termination

This study included an assessment of immunological effects in male mice. The assignment of mice to this segment of the study and the assays used are defined in the table below.

Group	Immunological Assay 1 Antibody Forming Cell Response to Sheep Erythrocytes[a]	Immunological Assay 2 Splenocyte Phenotyping and Anti-CD3 Proliferation Assay
Control	10 10 (cyclophosphamide positive control)[b]	10 10 (cyclophosphamide positive control)[b]

Group	Immunological Assay 1 Antibody Forming Cell Response to Sheep Erythrocytes	Immunological Assay 2 Splenocyte Phenotyping and Anti-CD3 Proliferation Assay
		10 (anti-asialo GM1 positive control)[c]
3 mg/kg	10	10
10 mg/kg	10	10
30 mg/kg	10	10

[a]All mice assigned to this assay group were sensitized with one iv administration of 0.2 mL of sheep RBCs 4 days prior to euthanasia.
[b]Mice received 50 mg/kg of cyclophosphamide ip for 4 consecutive days before being euthanised.
[c]Mice received 0.2 mL of a 1:10 dilution via iv injection.

Results

Mortality: No treatment-related deaths occurred during the study.

Clinical signs: No effects were observed.

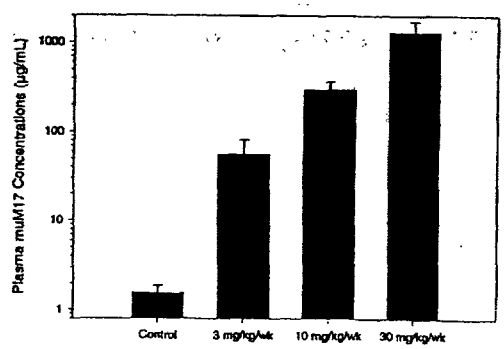
Body weight: No effects were observed.

Food consumption: This endpoint was not monitored

Hematology and clinical chemistry: WBC were increased ~2X in all groups due to an increase in both lymphocytes and neutrophils. Clinical chemistry values were generally comparable.

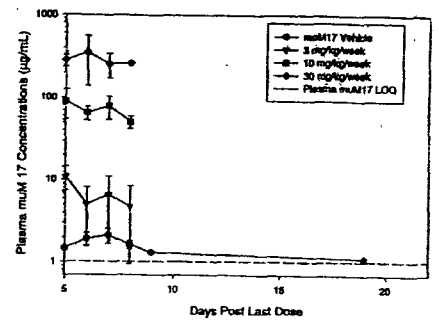
Toxicokinetics: Plasma levels at termination are shown in the charts below. In males, blood samples were collected 6 days after the last dose. In females, different conception days resulted in blood samples being collected 5 to 9 days after the last dose. (Charts were copied from the submission.)

Mean (±SD) Plasma muM17 Concentrations on Day 6 after the Last Dose following Four SC Doses of 0, 3, 10, or 30 mg/kg muM17 Before Cohabitation and Four Additional Doses after Cohabitation in Male Mice



Note: Limit of quantitation for muM17 in plasma was 1.0 µg/mL. Mice with LTR values were excluded from the mean and standard deviation calculations.

Mean (±SD) Plasma muM17 Concentrations following Three Subcutaneous Doses of 0, 3, 10, or 30 mg/kg muM17 Before Cohabitation and One Additional Dose after Confirmation of Mating in Pregnant Female Mice (4 Total Doses)



Note: Mice with LTR values were excluded from the mean and standard deviation calculations.

Immunogenicity: No antibodies to muM17 were detected in this study.

Necropsy: A single male in the high dose group had a visibly enlarged spleen. In contrast, females in all dose groups had visibly enlarged spleens (7/25, 5/25, and 7/25 for the 3, 10, and 30 mg/kg doses, respectively).

Organ weights: Treatment had no effect on male reproductive organs. Male mice exhibited increased spleen weight, but there was not a clearly defined dose response and the level of statistical significance was not consistently reached.

Fertility parameters (mating/fertility index, corpora lutea, preimplantation loss, etc.): The animals did not exhibit any treatment-related effects.

Immunotoxicity assessment

In Assay 1, the ability of mice to mount an immune response against sheep red blood cells was assessed by measuring the number of IgM-producing cells. As shown in the table below (Mean ± SE), treatment with muM17 had a marked effect on IgM production.

Treatment	IgM AFC/10^6 spleen cells	IgM AFC (X 10^3)/Spleen
Vehicle	1309 ± 376	234 ± 66
3 mg/kg muM17	65 ± 33*	15 ± 8*
10 mg/kg muM17	8 ± 4*	2 ± 1*
30 mg/kg muM17	54 ± 20*	14 ± 5*
50 mg/kg cyclophosphamide	0 ± 0*	0 ± 0*

*statistically significant

In Assay 2, treatment with muM17 had no readily apparent effect on splenocyte phenotype or anti-CD3-induced T-cell proliferation.

Embryofetal development

Study title: Subcutaneous developmental toxicity study of muM17 in mice

Key study findings: There were no embryofetal or maternal effects in this study. It is known from other studies that the doses used were pharmacologically active. muM17 was detected in the amniotic fluid at all doses.

Study no: 00-319-1049
Volume #, and page #: Not applicable (electronic submission)
Conducting laboratory and location: —

Date of study initiation: October 17, 2000
GLP compliance: Yes
QA report: yes (X) no ( )
Drug, lot #, and % purity: muM17 (murine surrogate for efalizumab), 34488-17

Methods

Doses: 0, 3, 10, and 30 mg/kg on gestation days (GD) 2, 9, and 16

Species/strain: Mouse, Crl: CD-1(—

Number/sex/group: 24 pregnant females

Route, formulation, volume, and infusion rate: sc; 0.3, 1.0, 3.0 mg muM17/mL; 10 mL/kg; bolus

Satellite groups used for toxicokinetics:

Study design:

Parameters and endpoints evaluated:

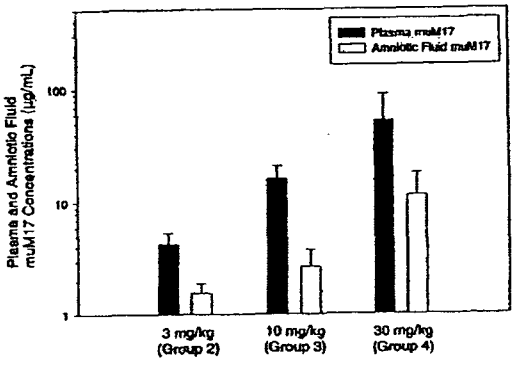
Toxicity was assessed as shown in the table below:

Endpoint	Timing
Viability	Daily
Observation	Daily
Body weight	Weekly
Necropsy	GD18
Caesarean section (# of corpora lutea, # and distribution of implantations, live and dead fetuses, early and late resorptions, fetal weight, fetal sex, gross external alterations, soft tissue alterations, and skeletal alterations)	GD18
Toxicokinetics (plasma and amniotic fluid)	GDs 0 (plasma) and 18 (plasma and amniotic fluid)
Immunogenicity	GDs 0 and 18

Results

Under the conditions of this study, there was no evidence of maternal or developmental toxicity. As shown in the chart below, plasma and amniotic fluid concentrations of muM17 increased in a dose proportional manner. No antibodies to muM17 were detected. (Chart was copied from the submission.)

Mean (±SD) Presumed Gestation Day 18 Plasma muM17 Concentrations Following Subcutaneous Administration on Days 2, 9, and 16



Study title: Pilot study: Subcutaneous developmental toxicity study of muM17 in mice

Key study findings: There were no embryofetal or maternal effects in this study. It is known from other studies that the doses used were pharmacologically active. muM17 was detected in the maternal plasma, amniotic fluid, and fetal plasma.

Study no: 00-342-1049
Volume #, and page #: Not applicable (electronic submission)
Conducting laboratory and location: —

Date of study initiation: August 3, 2000
GLP compliance: No
QA report: yes ( ) no (X)
Drug, lot #, and % purity: muM17, 34488-17

Methods

Doses: 50 mg/kg on gestation days (GD) 2, 9, and 16
Species/strain: Mouse, Crl: CD-1
Number/sex/group: 5 pregnant females
Route, formulation, volume, and infusion rate: sc; 3.0 mg/mL; 10 mL/kg; bolus
Satellite groups used for toxicokinetics: No
Study design: The goal of this study was to determine whether muM17 could cross the placenta. The females were treated sc with 50 mg/kg of muM17 on GD 2, 9, and 16. The dams underwent caesarian section on GD 18.
Parameters and endpoints evaluated: Maternal and fetal plasma and amniotic fluid samples were collected on GD18 and analyzed for muM17. Maternal plasma was also screened for antibodies to muM17.

Results

The plasma and amniotic fluid data, which indicate that muM17 crosses the placenta, are shown in the table below (mean ± SD).

Maternal plasma (ug/mL))	Amniotic fluid (ug/mL)	Fetal plasma (ug/mL)
82.1 ± 40.0	17.6 ± 4.85	79.1 ± 30.2

Analysis of maternal plasma did not reveal any antibodies to muM17.

Prenatal and postnatal development

Study title: Subcutaneous developmental and prenatal/postnatal reproduction toxicity study of muM17 in mice, including postnatal behavioral/functional and immunological evaluations

Key study findings: Treatment with muM17 had no effect on reproductive endpoints. In addition to assessing the effect of muM17 on reproductive function, the sponsor assessed the effect of treatment on the immune system of the F1 animals. At 11 weeks of age, F1 offspring born to dams treated with ≥ 3 mg/kg/week of muM17 from Gestation Day 2 through Lactation Day 21 exhibited a reduction (~35 to 80%) in their antibody response to sheep red blood cells, a T-cell dependent antigen. This reduction did not appear to be due to decreased number of T-cells or B-cells. A trend towards reversal was observed in F1 offspring at 25 weeks of age.

Study no.: 00-576-1049
Volume #, and page #: Not applicable (electronic submission)
Conducting laboratory and location:

Date of study initiation: February 2001
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: muM17, M3-TOX35

Methods

Doses: 0, 3, 10, and 30 mg/kg/week
Species/strain: Mouse, Crl: CD-1
Number/sex/group:

Generation	Group (mg/kg)	N
F_0	0	25F
	3	25F
	10	25F
	30	25F
F_1	0	95M/94F
	3	54M/55F
	10	54M/55F
	30	54M/52F

Route, formulation, volume, and infusion rate: sc; 0.3, 1.0, 3.0 mg muM17/mL; 10 mL/kg; bolus

Satellite groups used for toxicokinetics: No

Study design: F0 female mice were treated weekly from Gestation Day (GD) 2 through 22 (mice that did not deliver a litter) or Lactation Day (LD) 20 (mice that delivered a litter). The days of treatment were GD2, 9, 16, and 22 and LD 6, 13, and 20.

The F1 mice were not directly treated but might have been exposed during gestation or lactation.

On LD 21, the F1 mice were randomly divided into two subsets. The evaluations that each subset underwent are shown in the schematic below.

Parameters and endpoints evaluated:

Endpoint	Timing
F0	
Viability	Daily
Observation s	Daily
Body weight	Daily
Reproductive (# dams delivering, duration of gestation, implantation sites, mice with stillborn pups, mice with no live born pups, gestation index, pup survival)	Day of delivery through Day 21 of lactation.
Maternal behavior	LD 1, 4, 7, 14, and 21
Toxicokinetics	Not conducted
Milk sample analysis	Between LDs 12 and 17 post-partum (2 days after the 5th weekly administration)
Necropsy	LD21
F1	
Viability	At least 2X daily
Observations	Daily
Body weight	LD 1, 4, 7, 14, and 21
Toxicokinetics	At termination (~8 – 10 weeks after the last sc administration to the F0 dams)
Immunogenicity	At termination (~8 – 10 weeks after the last sc administration to the F0 dams)
F1 Subset 1	
Viability	At least 2X daily
Clinical observations	Weekly
Body weight	Weekly (M) Weekly during postweaning, on GD 0, 6, 12, and 18 after mating, and on LDs 1 and 4 after delivery of the F2
Sexual maturation	Beginning on day 6 of post-weaning
Passive avoidance	Beginning Day 2 post-weaning
Necropsy	LD21 (mice not selected for immunological tests) Day 154 post-weaning (mice assigned to immunoassay 1) Day 179 postweaning (mice assigned to immunoassay 2)
Organ weight (thymus, spleen, testes, epididymides)	At termination
Histopathology (thymus and mesenteric lymph nodes)	At termination
F1 Subset 2	
Viability	At least 2X daily
Observations	Weekly
Body weight	Weekly and at termination
F2	
Viability	2X daily
Observations	Daily
Body weight	LD1 and 4

Endpoint	Timing
Observation of nursing behavior	LD1 and 4
Sex determination	LD1 and 4
Termination	LD4

Immunotoxicity assessment in F_1:

Immunotoxicity was assessed in the F_1 generation at 11-weeks of age as indicated in the table below.

	Number of animals (11 weeks of age)					
	Assay 1 (IgM response) Ab-forming cell response to sheep erythrocytes[a]		Assay 1 (IgG response) Ab-forming cell response to sheep erythrocytes[b]		Assay 2 Splenocyte phenotyping, natural killer assay and anti-CD3 proliferation assay[c]	
F_0 muM17 (mg/kg)	Male	Female	Male	Female	Male	Female
0	10 + 10[d]	10 + 10[d]	10 + 10[d]	10 + 10[d]	10 + 10[d] + 10[e]	10 + 10[d] + 10[e]
3	10	10	10	10	10	10
10	10	10	10	10	10	10
30	10	10	10	10	10	10

[a]F1 mice were injected with sheep red blood cells (SRBCs) 4 days prior to euthanasia. Following euthanasia, the spleen IgM antibody response to SRBCs was assessed.
[b]F1 mice were injected with SRBCs 6 days prior to euthanasia. Following euthanasia, the spleen IgG response was assessed.
[c]Spleen cells were used to assess the effect of exposure during gestation and lactation on spleen cell phenotype, natural killer cell function, and anti-CD3-induced T cell proliferation.
[d]Cyclophosphamide (50 mg/kg; positive control) was administered ip for 4 consecutive days prior to euthanasia
[e]Anti-asialo GM1 (0.2 mL of a 1:10 dilution; positive control) was administered iv 24 hours before euthanasia.

Immunotoxicity was assessed in the F_1 generation at 25 weeks of age as indicated in the table below.

	Number of animals (25 weeks of age)			
	Assay 1 (IgM response) Ab-forming cell response to sheep erythrocytes[a]		Assay 2 Splenocyte phenotyping, natural killer assay and anti-CD3 proliferation assay[b]	
F_0 muM17 (mg/kg)	Male	Female	Male	Female
0	8 + 3[c]	8 + 3[c]	7 + 3[c]	7 + 2[c]
3	8 + 1[c]	8 + 1[c]	8	8 + 2[c]
10	8 + 1[c]	8 + 2[c]	8 + 2[c]	8 + 1[c]
30	8 + 1[c]	7	8 + 2[c]	7

[a]F1 mice were injected with sheep red blood cells (SRBCs) 4 days prior to euthanasia. Following euthanasia, the spleen IgM antibody response to SRBCs was assessed.
[b]Spleen cells were used to assess the effect of exposure during gestation and lactation on spleen cell phenotype, natural killer cell function, and anti-CD3-induced T cell proliferation.
[c]Cyclophosphamide (50 mg/kg; positive control) was administered ip for 4 consecutive

days prior to euthanasia

Results

F_0 in-life: Three deaths occurred in the 30 mg/kg group, one on GD10 and two on LD18. No cause of death was identified. The deaths are considered as possibly related to treatment.

The animals did not exhibit any treatment-related clinical signs.

Treatment had no effect on body weight.

Treatment had no effect on reproductive endpoints.

F_0 necropsy: The mice did not exhibit any treatment-related effects.

F_0 milk sample analysis: No muM17 was detected in the milk of dams receiving 3 or 10 mg/kg of muM17. In dams receiving 30 mg/kg, the concentration of muM17 in the milk was 16.3. ug/mL.

F_1 physical development: No treatment-related effects were observed.

F_1 behavioral evaluation: No treatment-related effects were observed.

F_1 reproduction: No treatment-related effects were observed.

F_1 organ weights: Absolute and relative spleen weight was significantly increased ~25 to 30% at all dose levels in male mice sacrificed at 25 weeks of age. No other organs were affected.

In female mice sacrificed at 25 weeks of age, the high dose group exhibited increased absolute (35%) and relative (38%) thymus weight. Spleen weight was not significantly affected.

F_1 histopathology: There were no muM17-related effects.

F_1 Immunological Testing: As shown in the table below exposure of the F1 offspring to muM17 *in utero* and lactation resulted in a marked decrease in their ability to produce IgM and IgG against sheep red blood cells, a T-cell dependent antigen.

Data (mean ± SE) below were obtained from animals at 11 weeks of age (* = statistically significant).

Treatment	Males (11 weeks old) Day 4 Response		Females (11 weeks old) day 4 response	
	IgM AFC/10^6 spleen cells	IgM AFC/Spleen ($X 10^3$)	IgM AFC/10^6 spleen cells	IgM AFC/Spleen ($X 10^3$)
Control	1131 ± 298	291 ± 93	921 ± 207	252 ± 53
muM17 3 mg/kg	498 ± 73	135 ± 20	375 ± 113*	93 ± 26*
muM17 10 mg/kg	719 ± 210	154 ± 37	517 ± 131	139 ± 34
muM17 30 mg/kg	198 ± 53*	51 ± 11*	267 ± 84*	69 ± 21*
Cyclophosphamide 50 mg/kg	4 ± 4*	1 ± 1	0 ± 0	0 ± 0

*Statistically significant

Treatment	Males (11 weeks old) Day 6 Response			
	IgM AFC/10^6 spleen cells	IgM AFC/Spleen ($X 10^3$)	IgG AFC/10^6 spleen cells	IgG AFC/Spleen ($X 10^3$)
Control	212 ± 90	42 ± 19	150 ± 49	29 ± 9
muM17 3 mg/kg	112 ± 18	24 ± 4	32 ± 17*	7 ± 4
muM17 10 mg/kg	95 ± 12	20 ± 2	80 ± 33	17 ± 7
muM17 30 mg/kg	83 ± 19*	18 ± 4	39 ± 12*	9 ± 3
Cyclophosphamide 50 mg/kg	0 ± 0*	0 ± 0	0 ± 0	0 ± 0

*Statistically significant

Treatment	Females (11 weeks old) Day 6 Response			
	IgM AFC/10^6 spleen cells	IgM AFC/Spleen ($X 10^3$)	IgG AFC/10^6 spleen cells	IgG AFC/Spleen ($X 10^3$)
Control	117 ± 21	28 ± 6	283 ± 82	68 ± 23
muM17 3 mg/kg	95 ± 12	21 ± 3	70 ± 21*	14 ± 4*
muM17 10 mg/kg	112 ± 18	22 ± 4	67 ± 37*	14 ± 8*
muM17 30 mg/kg	79 ± 22	16 ± 5	96 ± 42*	19 ± 9*
Cyclophosphamide 50 mg/kg	1 ± 1*	1 ± 1	0 ± 0*	0 ± 0*

*Statistically significant

In animals 25 weeks of age, the IgM response was decreased. However, the magnitude of the decrease was not as pronounced as that seen in the 11 week old mice, and the differences between the control and treated animals did not reach the level of statistical significance. Data are mean ± SE.

Treatment	Males (25 weeks old) Day 4 Response		Females (25 weeks old) day 4 response	
	IgM AFC/10^6 spleen cells	IgM AFC/Spleen ($X 10^3$)	IgM AFC/10^6 spleen cells	IgM AFC/Spleen ($X 10^3$)
Control	1345 ± 327	314 ± 69	1559 ± 542	328 ± 103
muM17 3 mg/kg	1016 ± 272	284 ± 68	972 ± 344	222 ± 76
muM17 10 mg/kg	1344 ± 373	286 ± 73	855 ± 289	252 ± 85
muM17 30 mg/kg	831 ± 184	191 ± 45	817 ± 342	179 ± 64

F1 toxicokinetics and immungenicity: No plasma levels of muM17 were detected. Similarly, no antibodies to muM17 were detected.

F_2 findings: The F2 pups did not exhibit any effects.

3.4.7 Local tolerance In accordance with ICH S6, Preclinical Safety Evaluation of biotechnology-Derived Pharmaceutical", local tolerance was addressed as part of another study.

3.4.8 Special toxicology studies

Study title: Subcutaneous immunotoxicology study of muM17 in mice

Key study findings: All dose groups exhibited increased splenic lymphocytes, a marked decreases (≥ 90%) in IgM response to a T cell dependent antigen, and decreased NK cell activity (48% to 68% and 71% to 88% in males and females, respectively). In males, the effects on spleen cell numbers fully reversed and the effect on IgM partially reversed. In contrast, reversal of the effect on NK cell activity was not observed. All effects were reversed in the female recovery group.

Study no.: 01-273-1049
Volume #, and page #: Not applicable (electronic submission)
Conducting laboratory and location: [redacted]

Date of study initiation: December 2001
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: muM17, M3-TOX35
Formulation/vehicle: 0.3, 1, and 3 mg/mL

Methods

Doses: 0, 3, 10 and 30 mg/kg/week (Days 1, 8, 15, and 22 of the study)
Species/strain: Mouse, Crl: CD-1
Number/sex/group or time point (main study): Contol = 74M and 76F; 3 mg/kg = 46/sex; 10 and 30 mg/kg = 20/sex
Route, formulation, volume, and infusion rate: sc; 0.3, 10, and 3.0 mg/mL; 10 mL/kg; bolus
Satellite groups used for toxicokinetics or recovery: None
Age: 58 days
Weight (nonrodents only): NA
Unique study design or methodology (if any): The study was conducted using muM17, the murine surrogate for efalizumab.

The mice were treated with muM17 on Days 1, 8, 15, and 22 of the study. The number of animals used in this study is shown in the table below.

	Number of animals					
	Assay 1 (1° response)		Assay 1 (2° response)		Assay 2	
	Ab-forming cell response to sheep erythrocytes[a]		Ab-forming cell response to sheep erythrocytes[b]		Splenocyte phenotyping, natural killer assay and anti-CD3 proliferation assay[c]	
muM17 (mg/kg)	Male	Female	Male	Female	Male	Female
0	10 + 6[d] + 10[b]	10 + 6[d] + 10[e]	8 + 6[d]	8 + 6[d]	10 + 6d + 10[e] + 6[f]	10 + 6[d] + 10[e] + 6[f]
3	10 + 6[d]	10 + 6[d]	8 + 6[d]	8 + 6[d]	10 + 6[d]	10 + 6[d]
10	10	10	-	-	10	10
30	10	10	-	-	10	10

[a] All mice assigned to assay 1 (1° response) were sensitized with an iv injection of sheep RBCs (SRBCs) four days prior to euthanasia.
[b] All mice assigned to assay 2 (2° response) were sensitized with SRBCs.
[c] The mice assigned to assay 2 did not receive any sheep SRBCs.
[d] Mice assigned to recovery
[e] Cyclophosphamide (positive control)
-administered as a 50 mg/kg/day ip injection for four days prior to euthanasia
[f] Anti-asialo gm1 (positive control) 0.2 ml of a 1:10 dilution was administered iv ~ 24 hours before euthanasia.

Study design:

The endpoints monitored in this study are as follows.

Endpoint	Timing
Viability	2X daily
Observations	Weekly
Body weight	Weekly
Hematology	Prior to dosing Termination
Termination	Terminal sacrifice: 1 week after the last dose (Day 28 or 29) Recovery sacrifice: Day 50
Histopathology	At termination (limited to gross lesions, thymus, and mesenteric lymph node)
Bone marrow	At termination
Immunological evaluations	Spleen IgM response to T-dependent Ag (sheep RBCs) Spleen IgG response to T dependent Ag (sheep RBCs) Splenocyte phenotyping Natural Killer cell assay Spleen cell proliferative response to anti-CD3 mediated T cell proliferation
Toxicokinetics and immunogenicity	Prior to treatment (terminal and recovery groups) One week after the last dose (terminal and recovery groups) Day 50 (recovery group)

Results:

Viability: There were no treatment-related deaths.

Observations: The animals did not exhibit any treatment-related effects.

Body weight: The animals did not exhibit any toxicologically relevant effects.

Hematology: Although the mice exhibited effects associated with muM17 in the repeat dose toxicology studies (↑ WBCs, neutrophils, and lymphocytes and ↓ platelets), the effect was not as well defined as in the previous studies.

Gross pathology: The animals did not exhibit any effects.

Organ weights (specify organs weighed if not in histopath table): Although spleen weight was increased in males (~6.5% to 17%) and females (~9% to 17%), the differences did not exhibit a dose-response and did not reach the level of statistical significance.

Histopathology: Adequate Battery: yes (X), no ( )—explain
Peer review: yes ( ), no ( )

The animals did not exhibit any muM17-related effects.

Bone marrow: The animals did not exhibit any muM17-related effects.

Immunological evaluations: These were conducted on the spleens obtained from control and treated animals.

Spleen IgM response to T-dependent Ag (sheep RBCs): In male mice treated with muM17, IgM AFC/10^6 spleen cells and IgM/spleen were reduced to 3 to 5% of the control level in all treatment groups at the end of the treatment period. In female mice treated with muM17, IgM AFC/10^6 spleen cells and IgM/spleen were reduced to 6 to 12% of the control level in all treatment groups at the end of the treatment period.

Following the treatment-free recovery period, the IgM response in the male mice remained below the control level (28% and 36% for IgM/ 10^6 spleen cells and IgM/spleen, respectively), but the difference was not statistically significant. In contrast, females exhibited an increase in IgM response (43% and 33% for IgM/ 10^6 spleen cells and IgM/spleen, respectively).

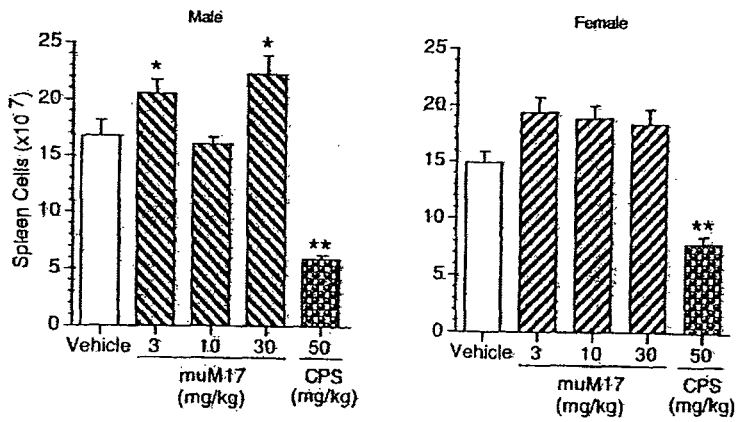
Spleen IgG response to T-dependent Ag (sheep RBCs): The IgG response was less affected by muM17 treatment in both genders. In male mice treated with muM17, IgG AFC/10^6 spleen cells and IgG/spleen were reduced to ~40% of the control level in the 3 mg/kg group (the only group evaluated for this response) at the end of the treatment period. In female mice treated with muM17, IgG AFC/10^6 spleen cells and IgG/spleen were reduced to 60 to 70% of the control level in the 3 mg/kg treatment group (the only group evaluated for this response) at the end of the treatment period.

Following the treatment-free recovery period, the IgG response in the male mice

remained below the control level (~75% for IgG/ 10^6 spleen cells and IgG/spleen), but the decrease was not statistically significant. In contrast, females exhibited an increase in IgG response (81% and 44% for IgG/ 10^6 spleen cells and IgG/spleen, respectively).

Splenocyte phenotyping: In general, muM17 treatment increased (~20 to 30%) spleen cell number in all groups, but the level of statistical significance was not always reached. This effect was reversible in the recovery subset. (The charts were copied from the submission.)

Figure 1
Spleen Cell Number in Male and Female CD-1 Mice Treated with muM17 Weekly for 4 Weeks



Treatment with muM17 resulted in changes in splenic lymphocyte populations. Differences were observed between males and females with regard to the magnitude of the change and whether the changes were statistically significant. Example data are shown in the charts below. (The charts were copied from the submission.)

Figure 2
CD3+ and CD4+CD8- Splenic Surface Markers in Male CD-1 Mice Treated with muM17 Weekly for 4 Weeks

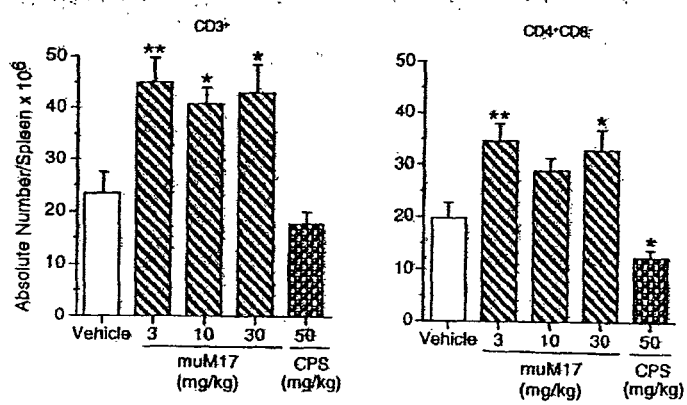
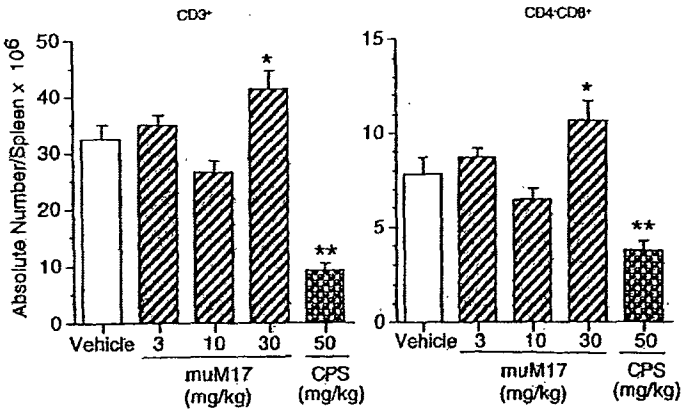


Figure 3
CD3+ and CD4-CD8+ Splenic Surface Markers in Female CD-1 Mice
Treated with muM17 Weekly for 4 Weeks



Natural killer cell assay: NK cell activity was suppressed at all dose levels in males (48% to 68%) and females (71% to 88%).

At the end of the recovery period, NK cell activity in males remained decreased (~60%) relative to the control group. In contrast, NK cell activity in the female recovery mice did not differ from that observed in the control group.

Spleen cell proliferative response to anti-CD3-mediated T cell proliferation: In male and female mice, T-cell proliferation was increased relative to the control group (~40% and ~65%, respectively), but the difference was statistically significant in females only. This effect was reversible following the treatment-free recovery period.

Toxicokinetics: Plasma levels of muM17 in samples collected on Day 29, 7 days after the last dose, are shown in table below. Data are expressed as ug/mL (± SD). On Day 50, plasma levels were less than reportable in the recovery group.

Group	Dose (mg/kg/week)	Males	Females
1	0	---	---
2	3	34.1 (13.5)	30.2 (15.6)
2 (recovery)	3	38.0 (7.85)	28.2 (11.8))
3	10	220 (96)	366 (184)
4	30	587 (118)	596 (88.8)

Immunogenicity: No antibodies to muM17 were detected.

Study title: hu1124: A 2-day investigative intravenous infusion toxicology study in chimpanzees

Key study findings: Findings, including decreased expression of CD11a, did not differ from those observed in the control. Based on an absence of efalizumab in the control chimpanzee, it is assumed that animal was not inadvertently dosed with efalizumab.

Study no.: 970609
Volume #, and page #: Not applicable (electronic submission)
Conducting laboratory and location: [redacted]

Date of study initiation: May 1997
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: hu1124, GC609003-5,
Formulation/vehicle: 4 mg/mL

Methods

Doses: 0 and 40 mg/kg/day X 2 days
Species/strain: Chimpanzee
Number/sex/group or time point (main study): 0 = 1 male; 40 mg/kg = 2 males
Route, formulation, volume, and infusion rate: iv; 4 mg/mL; 10 mL/kg; infusion
Satellite groups used for toxicokinetics or recovery: None
Age: 11 to 32 years
Weight (nonrodents only): 47.2 to 57.4 kg
Unique study design or methodology (if any):

Study design: The endpoints monitored in this study are defined in the table below.

Endpoint	Timing
Body weights	Pretreatment Daily on each treatment day 1 day after treatment
Physical exams (Vital signs, ECG, pulse rate, respiratory rate, and systolic and diastolic blood pressures)	Pretreatment Daily on each treatment day 1 day after treatment
Ophthalmology	Pretreatment and Day 1
Body temperature	1 day prior to infusion Immediately prior to infusion 2, 4, 6, 8 and 12 hours after infusion on Days 1 and 2 24 hours after the end of the second infusion
Observations	Daily
Food consumption	Daily
Clinical chemistry and hematology	Pretreatment Days 1 + 2 (0, 2, 4 and 8hr each day) and 3
Coagulation factors	Pretreatment Days 1(4 hr), 2 (0 + 4 hr), 3
Flow cytometry (expression of CD11a)	Pretreatment 4, 24, 28, and 48 hours after infusion on Day 1
Cerebral spinal fluid	24 hours following the second dose
Toxicokinetics	One day prior to treatment Prior to and at the end of infusion 2 hours after the end of infusion Day 3

Results:

Body weight: Body weight was decreased in all animals. The author of the study report attributed this effect was "likely associated with the extensive amount of anesthesia utilized during the study period". However, no details regarding anesthesia were provided in the study report.

Physical exams: The animals did not exhibit any treatment-related effects.

Body temperatures: All animals showed fluctuations in body temperature. The increases observed in the control animals exceeded those observed in the treated animals.

Clinical pathology: The animals did not exhibit any treatment-related effects.

Flow cytometry: CD11a expression was decreased in all animals including the control. There is no explanation for the decrease observed in the control animal.

Cerebral spinal fluid: The animals did not exhibit any treatment-related effects.

Toxicokinetics: No efalizumab was detected in the control animal or in any animal prior to infusion. The 2 treated animals exhibited significant exposure to hu1124.

Study title: **hu1124: A 2-day investigative intravenous infusion toxicology study with implantable temperature transponder microchips in chimpanzees**

Key study findings: .

Study no.: 970909
Volume #, and page #: Not applicable (electronic submission)
Conducting laboratory and location:

Date of study initiation: August 1997
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: hu1124, GC609003-6,
Formulation/vehicle: 4 mg/mL

Methods

Doses: 0 and 40 mg/kg/day X 2 days
Species/strain: Chimpanzee
Number/sex/group or time point (main study): 0 = 1 male; 40 mg/kg =3 males
Route, formulation, volume, and infusion rate: iv; 4 mg/mL; 10 mL/kg; infusion
Satellite groups used for toxicokinetics or recovery: None
Age: 10 to 32 years

Weight (nonrodents only): 44.9 to 54.0 kg
Unique study design or methodology (if any): None

Study design: The endpoints monitored in this study are defined in the table below.

Endpoint	Timing
Body weights	Pretreatment Daily on each treatment day 1 day after treatment
Physical exams (Vital signs, general ophthalmic exam, ECG, pulse rate, respiratory rate, and systolic and diastolic blood pressures)	Pretreatment Daily on each treatment day 1 day after treatment
Body temperature	Prior to infusion Every 15 – 30 minutes during infusion 2, 4, 6, 8, 10 and 12 hours after infusion on Days 1 and 2 24 hours after the end of the second infusion
Observations	Daily
Food consumption	Daily
Clinical pathology (clinical chemistry, hematology, coagulation factors)	Pretreatment Days 1, 2, 3, and 9
Flow cytometry (expression of CD11a)	Pretreatment 4, 24, 28, and 48 hours after infusion on Day 1
Cerebral spinal fluid	24 hours following the second dose
Toxicokinetics	One day prior to treatment Prior to and at the end of infusion 2 hours after the end of infusion Day 3

Results:

Body weight: Body weight was decreased in all animals. The author of the study report attributed this effect was "likely associated with study procedures, including fasting and anesthesia during the study period". However, no details regarding anesthesia were provided in the study report.

Physical exams: The animals did not exhibit any treatment-related effects.

Body temperatures: Body temperature was assessed rectally and using implanted microchips. However, microchip data were available for Day 1 only. There was no clear between the response observed in the treated animals and that observed in the controls.

Clinical pathology: The animals did not exhibit any treatment-related effects.

Flow cytometry: CD11a expression was decreased in the animals receiving efalizumab.

Cerebral spinal fluid: The animals did not exhibit any treatment-related effects.

Toxicokinetics: No hu1124 was detected in the control animal or in any animal prior to infusion. The 3 treated animals exhibited significant exposure to efalizumab. Lower levels of efalizumab were detected in the CSF of all treated animals.

Study title: Cross reactivity of biotinylated humanized monoclonal antibody hu1124 with normal tissues

Key study findings: The pattern of staining observed with efalizumab was consistent with the known distribution of CD11a-expressing cells.

Study no.: IM296
Volume #, and page #: Not applicable (electronic submission)
Conducting laboratory and location:

Date of study initiation: August 1996
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: efalizumab
Formulation/vehicle: 1 ug/mL and 10 ug/mL in phosphate-buffered saline

Methods:

Doses: 1 ug/mL and 10 ug/mL

Study design: Efalizumab was tested as its biotinylated derivative in a battery of normal human tissues at protein concentrations of 1.0 and 10.0 ug/mL. Tissues were tested in triplicate. Human IgG1 served as the negative control antibody. The positive control tissue was CD11a-expressing Jukrat cells.

Results: The pattern of staining observed with efalizumab was consistent with the expected distribution of CD11a. Staining was observed with the following tissues: blood lymphocytes and monocytes in blood smears and in most organs, stromal cells of the connective tissue of most organs and intraepithelial cells of many organs (considered to be dendritic cells or intraepithelial leukocytes), and T-dependent areas of lymphoid tissues.

Staining, which was considered to be microglial in origin, was observed in the perivascular adventitia of cerebrum cerebellum, and spinal cords from 1/3 samples from unique donors. In all cells, binding was primarily on the cell membrane and less intensely on the cytoplasmic structures.

Study title: Cross reactivity of hu1124 with normal human cranial nerves and inner ear

Key study findings: During clinical trials with efalizumab, a single incidence of unilateral hearing loss was observed in one patient. In order to address this finding, the cross reactivity study with cranial and the inner ear was conducted. Staining was limited to cells reported in the literature to express CD11a. Staining with other structures was not observed.

Study no.: IM534
Volume #, and page #: Not applicable (electronic submission)
Conducting laboratory and location: [redacted]

Date of study initiation: July 7, 1999
GLP compliance: yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: hu1124(eflaizumab); lot # MW960711; purity not provided
Formulation/vehicle: 1.31 mg protein/mL

Methods

Doses: 1 and 10 ug/mL

Study design: Efalizumab was tested as its biotinylated derivative in sections of human optic chiasm, acoustic nerve, and inner ear at protein concentrations of 1.0 and 10.0 ug/mL. Human IgG1 served as the negative control antibody. The positive control tissue was CD11a-expressing Jukrat cells.

Results: Staining was limited to cells reported in the literature to express CD11a. Staining with other structures was not observed.

Study title: Cross reactivity of biotinylated humanized monoclonal antibody hu1124 with normal chimpanzee (Pan troglodytes) tissues

Key study findings: The pattern of staining was consistent with the known distribution of CD11a and was comparable to that observed with human tissues. The data from this study support the use of the chimpanzee as a relevant model for humans.

Study no.: IM297
Volume #, and page #: Not applicable (electronic submission)
Conducting laboratory and location: [redacted]

Date of study initiation: August 14, 1996
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, and % purity: hu1124; lot# MW960711, purity not provided
Formulation/vehicle: 1.31 mg protein/mL

Methods

Doses: 1 and 10 ug/mL

Study design: Efalizumab(hu1124) was tested as its biotinylated derivative in a battery of normal chimpanzee tissues at protein concentrations of 1.0 and 10.0 ug/mL. Human IgG1 served as the negative control antibody. The positive control tissue was CD11a-expressing Jukrat cells.

Results: The pattern of staining was consistent with the known distribution of CD11a and was comparable to that observed with human tissues.

Study title: Cross-reactivity of murine anti-mouse CD11a monoclonal antibody (muM17) with normal mouse tissue

Key study findings: The distribution of CD11a to CD1 mouse tissues was similar to that observed with human and chimpanzee tissues with the exception of the intestinal epithelial and optic nerve meninges, which were stained with the mouse antibody only.

Study no.: IM554
Volume #, and page #: Not applicable (electronic submission)
Conducting laboratory and location: —

Date of study initiation: January 14, 2000
GLP compliance: Yes
QA reports: yes (Y) no ( )
Drug, lot #, and % purity: muM17; lot # 1201-26; purity not provided
Formulation/vehicle: 5.33 mg protein/mL

Methods

Doses: 1 and 10 ug/mL

Study design:: muM17 was tested as its biotinylated derivative in a battery of normal CD1 mouse tissues at protein concentrations of 1.0 and 10.0 ug/mL. Murine IgG1 served as the negative control antibody. Mouse spleen was used as the positive control tissue.

Results: The distribution of CD11a to CD1 mouse tissues was similar to that observed with human and chimpanzee tissues with the exception of the intestinal epithelial and optic nerve meninges, which were stained with the mouse antibody only. These results support the use of muM17 as an appropriate surrogate for efalizumab.

3.6 OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: The results of the nonclinical pharmacology/toxicology studies that the sponsor submitted adequately support the approval of RAPTIVA for use in psoriasis. The effects observed in the nonclinical studies reflect the intended pharmacological effect of the product. The nonclinical issues relevant to clinical use are [1] decreased ability of efalizumab-treated chimpanzees to mount an immune response to tetanus toxoid when CD11a expression is decreased, and [2] diminished ability of mouse pups born to dams treated with muM17 during gestation and lactation to mount an immune response to a T cell dependent antigen. These concerns have been discussed with the clinical review staff and are being addressed through labeling and/or post-marketing commitments.

Unresolved toxicology issues (if any): There are no unresolved toxicology issues.

Recommendations: None

Suggested labeling:

PRECAUTIONS

[

]

Genotoxicity studies were not conducted.

Pregnancy Category C

Animal reproduction studies have not been conducted with RAPTIVA. It is also not known whether RAPTIVA can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. RAPTIVA should be given to a pregnant woman only if clearly needed.

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Nursing Mothers

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Signatures (optional):

Reviewer Signature /S/ 10-23-03

Supervisor Signature /S/ 10-23-03 Concurrence Yes ✓ No ___

3.7. APPENDIX/ATTACHMENTS

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Appendix 2
Studies reviewed within this submission
(Copied from the submission.)

The studies reviewed within this submission are shown below. In addition to those studies the following study was reviewed: Study 01-292-1049, A six month subcutaneous toxicology study of muM17 in TSGp53® wild type mice.

4. Nonclinical Study Reports

4.1 Nonclinical Study Reports Table of Contents

4.2 Study Reports

4.2.1 Pharmacology

4.2.1.1 Primary Pharmacodynamics

00-118-1046: Compare rhuMAb CD11a from Genentech and from XOMA for Binding to Human and Chimpanzee T-Lymphocytes

00-174-1046: In Vitro Modulation of CD11a on Human T Cells with XOMA and Genentech Anti-CD11a

01-404-1049: Effect of Efalizumab in a Human One-Way Mixed Lymphocyte Reaction (MLR)

01-436-1049: Effect of Efalizumab on T-Cell Activation

01-263-1046: Effect of Xanelim™ (Efalizumab) on the Adhesion of Human T Lymphocytes to Endothelial Cells

01-426-1046: Effect of Xanelim™ (Efalizumab) on the Adhesion of Human T Lymphocytes to Keratinocytes

01-437-1049: Effect of Efalizumab on Transendothelial Migration of T Cells

91-328-1049: Expression of Lymphocyte Adhesion Molecules in Psoriatic Skin and the Effects of Anti-LFA-1

01-427-1046: Anti-CD11a Ameliorates Disease in the Human Psoriatic Skin–SCID Mouse Transplant Model: Comparison of Antibody to CD11a with Cyclosporin A and Clobetasol Propionate

01-143-1049: Comparative Binding Affinities of Xanelim™ (Efalizumab), muM17 and M17

01-142-1049: Effect of the muM17 Antibody on a Mixed Lymphocyte Reaction

01-245-1049: Assessment of Cell-Mediated Immune Function in Mice Treated with muM17

01-319-1049: Assessment of Cell-Mediated Immune Function in TSG-p53® Wild Type Mice Treated with muM17

00-520A-1047: Multiple Dose Percent Saturation and Toxicokinetics of an Anti-Mouse CD11a (muM17) Antibody in Female CD-1 Mice

TABLE OF CONTENTS (cont'd)

4.2.2.4 Metabolism

02-328-1046: Internalization and Clearance of a Murine Antibody Specific for Mouse CD11a

4.2.2.5 Excretion

4.2.2.6 Pharmacokinetic Drug Interactions

4.2.2.7 Other Pharmacokinetic Studies

99-538A-1046: Pharmacokinetics of Anti-CD11a (XOMA Formulation) in Rabbits following Intravenous Administration

99-214-1046: Pharmacokinetics of XOMA hu1124 (Anti-CD11a) in Rabbits

00-119-1046 & 00-119A-1046: Comparability Pharmacokinetics of Anti-CD11a (Genentech vs. XOMA Formulation) in Rabbits

01-260-1046: Comparability Pharmacokinetics of Humanized Anti-CD11a (Genentech vs. XOMA Formulation) in Rabbits

00-092-1046: A Single-Dose Subcutaneous Study to Evaluate the Pharmacokinetics and Pharmacodynamics of Two Formulations of Humanized Anti-CD11a in a Chimpanzee Model

02-223-1046: Effects of Glycosolation on the Pharmacokinetics of muM17 following a Single Dose in Mice

02-224-1046: Effects of Glycosolation and Formulation on the Pharmacokinetics of muM17 following a Single Dose in Mice

4.2.3 Toxicology

4.2.3.1 Single-Dose Toxicity

00-299-1047: Effect of an Anti-Mouse CD11a (muM17) Antibody on White Blood Cell Counts and Differentials in Female CD-1 Mice

4.2.3.2 Repeat-Dose Toxicity

960809: hu1124: A 5-Day Intravenous Dose-Range Finding Study in Chimpanzees

961109: hu1124: An Intravenous Repeated-Dose Safety/Toxicity Study with a Reversibility Phase in Chimpanzees

980309: hu1124: A Single-Dose Re-Exposure Safety Study in Chimpanzees

99-362-1047: Multiple Dose Safety and Toxicokinetics of an Anti-Mouse CD11a (muM17) Antibody in Female CD-1 Mice

00-297-1047: Multiple Dose Safety and Toxicokinetics of an Anti-Mouse CD11a (muM17) Antibody in Female CD-1 Mice

01-229-1049: A One-Month Subcutaneous Toxicology Study of muM17 in TSG-p53® Wild Type Mice

4.2.3.3 Genotoxicity
- 4.2.3.3.1 In Vitro
- 4.2.3.3.2 In Vivo

4.2.3.4 Carcinogenicity
- 4.2.3.4.1 Long-Term Studies
- 4.2.3.4.2 Short- or Medium-Term Studies
- 4.2.3.4.3 Other Studies

4.2.3.5 Reproductive and Developmental Toxicity
- 4.2.3.5.1 Fertility and Early Embryonic Development
  - 00-342-1049: Pilot Study: Subcutaneous Developmental Toxicity Study of muM17 in Mice
  - 01-006-1049: Subcutaneous Fertility and General Reproduction Toxicity Study of muM17 in Mice, Including Immunological Evaluations
- 4.2.3.5.2 Embryo-Fetal Development
  - 00-319-1049: Subcutaneous Developmental Toxicity Study of muM17 in Mice
- 4.2.3.5.3 Prenatal and Postnatal Development, Including Maternal Function
  - 00-576-1049: Subcutaneous Developmental and Perinatal/Postnatal Reproduction Toxicity Study of muM17 in Mice, Including Postnatal Behavioral/Functional and Immunological Evaluations
- 4.2.3.5.4 Studies in Which the Offspring (Juvenile Animals) Are Dosed and/or Further Evaluated

4.2.3.6 Local Tolerance

4.2.3.7 Other Toxicity Studies
- 4.2.3.7.1 Antigenicity
  - 01-273-1049: Subcutaneous Immunotoxicology Study of muM17 in CD-1 Mice
- 4.2.3.7.2 Immunotoxicity
- 4.2.3.7.3 Mechanistic Studies
- 4.2.3.7.4 Dependence
- 4.2.3.7.5 Metabolites
- 4.2.3.7.6 Impurities

4.2.3.7.7 Other

IM534: Cross-Reactivity of hu1124 with Normal Human Cranial Nerves and Inner Ear

IM297: Cross-Reactivity of Biotinylated Humanized Monoclonal Antibody hu1124 with Normal Chimpanzee (Pan Troglodytes) Tissues

IM296: Cross-Reactivity of Biotinylated Humanized Monoclonal Antibody hu1124 with Normal Tissues

99-390-1049: Cross-Reactivity of Murine Anti-Mouse CD11a Monoclonal Antibody (muM17) with Normal Mouse Tissue

970609: hu1124: A 2-Day Investigative Intravenous Infusion Toxicology Study in Chimpanzees

970909: hu1124: A 2-Day Investigative Intravenous Infusion Toxicology Study with Implantable Temperature Transponder Microchips in Chimpanzees

4.3 Publications

Appendix 3
Studies not reviewed within this submission
(Copied from the submission)

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Appendix 4
Pharmacokinetics and toxicokinetics summary tables
(Copied from the submission)

Table 2.6.5.2
Efalizumab Single-Dose Noncompartmental Pharmacokinetic Parameters in the Rabbit: Intravenous and Subcutaneous Routes of Administration

Species/ Strain	Dose (mg/kg)	Study	Product Code (Material)	No./ Sex/ Group	C_{max} (µg/mL)	t_{max} (day)	AUC_{last} (µg • day/mL)	CL or CL/F[a] (mL/kg/day)	V_{ss} or V/F[b] (mL/kg)	$t_{1/2z}$ (days)	F (%)
Intravenous Route											
Rabbit/ NZW	2	99-538A-1046	102515 (XOMA)	5/M	32.9 ± 2.66	NC	137 ± 20.2	13.9 ± 3.24	152 ± 25.8	9.74 ± 3.58	NC
Rabbit/ NZW	2	00-119-1046; 00-119A-1046	G176H (GNE)	6/M	19.8 ± 1.51[c]	NC	86.5 ± 17.3[d]	11.8 ± 2.59	121 ± 27.9	8.20 ± 3.93	NC
Rabbit/ NZW	2	00-119-1046; 00-119A-1046	102646 (XOMA)	6/M	18.5 ± 1.95[c]	NC	74.6 ± 7.15[d]	13.3 ± 1.32	145 ± 14.8	8.83 ± 1.65	NC
Subcutaneous Route											
Rabbit/ NZW	0.2	99-214-1046	102646 (XOMA)	5/M	1.04 ± 0.060	3.00 ± 0.710	10.0 ± 2.30	16.2 ± 1.38	128 ± 30.6	5.62 ± 1.70	NC
Rabbit/ NZW	0.5	01-260-1046	G176H (GNE)	6/M	7.42 ± 0.680	2.50 ± 0.840	101 ± 10.4	9.84 ± 0.960	124 ± 13.0	8.76 ± 0.700	NC
Rabbit/ NZW	0.5	01-260-1046	102646 (XOMA)	5/M	7.64 ± 0.380	3.20 ± 0.840	102 ± 20.9	10.1 ± 2.88	126 ± 38.5	9.49 ± 3.88	NC
Rabbit/ NZW	1	01-260-1046	G176H (GNE)	4/M	8.21 ± 0.570	3.50 ± 1.00	99.9 ± 18.6	9.51 ± 1.17	120 ± 27.2	8.88 ± 2.37	NC
Rabbit/ NZW	1	01-260-1046	102646 (XOMA)	5/M	7.71 ± 1.07	3.00 ± 0.710	100 ± 25.9	10.6 ± 3.82	119 ± 26.4	8.73 ± 3.21	NC
Rabbit/ NZW	2	99-214-1046	102646 (XOMA)	5/M	11.0 ± 1.11	2.80 ± 0.840	118 ± 32.8	14.9 ± 3.62	129 ± 28.4	6.23 ± 1.89	NC
Rabbit/ NZW	2	00-119-1046; 00-119A-1046	G176H (GNE)	8/M	6.43 ± 0.58[c]	4.00 ± 2.37	84.5 ± 19.4[d]	12.4 ± 3.47	111 ± 33.6	6.92 ± 3.29	97.6 ± 22.3

Table 2.6.5.2 (cont'd)
Efalizumab Single-Dose Noncompartmental Pharmacokinetic Parameters in the Rabbit:
Intravenous and Subcutaneous Routes of Administration

Species/ Strain	Dose (mg/kg)	Study	Product Code (Material)	No./ Sex/ Group	C_{max} (µg/mL)	t_{max} (day)	AUC_{last} (µg • day/mL)	CL or CL/F[a]	V_{ss} or V/F[b]	$t_{1/2z}$ (days)	F (%)
Subcutaneous Route (cont'd)											
Rabbit/ NZW	2	00-119-1046; 00-119A-1046	102646 (XOMA)	8/M	6.98 ± 2.20[c]	2.63 ± 1.06	81.5 ± 26.3[d]	13.4 ± 4.77	128 ± 30.1	7.26 ± 2.30	109 ± 35.2
Rabbit/ NZW	2	01-260-1046	G176H (GNE)	6/M	7.46 ± 1.12	3.17 ± 0.980	101 ± 23.7	10.3 ± 2.57	123 ± 13.4	8.61 ± 1.82	NC
Rabbit/ NZW	2	01-260-1046	102646 (XOMA)	5/M	8.23 ± 0.670	3.40 ± 0.550	105 ± 18.8	9.71 ± 2.12	126 ± 32.7	9.18 ± 2.54	NC
Rabbit/ NZW	20	99-214-1046	102646 (XOMA)	5/M	96.3 ± 7.72	3.40 ± 0.550	860 ± 65.9	20.1 ± 2.09	134 ± 39.9	4.72 ± 1.71	NC

GNE = Genentech.

M = Male.

NC = Not calculated.

NZW = New Zealand White.

[a] CL was calculated for the IV dose group, and CL/F was calculated for the SC dose group.

[b] V_{ss} was calculated for the IV dose group, and V/F was calculated for the SC dose group.

[c] C_{max}/dose value reported.

[d] AUC_{last}/dose value reported.

Table 2.6.5.3
Efalizumab Single-Dose Noncompartmental Pharmacokinetic Parameters in the Chimpanzee: Intravenous and Subcutaneous Routes of Administration

Species/ Strain	Dose (mg/kg)	Study	Product Code (Material)	No./ Sex/ Group	C_{max} (µg/mL)	t_{max} (day)	AUC_{last} (µg • day/mL)	CL or CL/F[a] (mL/kg/day)	V_{ss} or V_z/F[b] (mL/kg)	$t_{1/2z}$ (days)	F (%)
Intravenous Route											
Chimpanzee/ Pan troglodyte	0.51	8758-9810[c]	102515 (XOMA)	1/M 1/F	10.8[d]	NC	12.7[e]	78.5	84.5	0.69[f]	NC
Chimpanzee/ Pan troglodyte	0.50	8758-9810[g]	102515 (XOMA)	1/M 1/F	17.3[d]	NC	18.3[e]	55.7	47.8	0.69[f]	NC
Chimpanzee/ Pan troglodyte	2	980309	102515 (XOMA)	1/M, 1/F	21.3[d]	NC	69.5[e]	14.7	68.1	2.51[f]	NC
Chimpanzee/ Pan troglodyte	10	960809	102479 (XOMA)	1/M, 1/F	27.3[d]	NC	138[e]	7.67	85.1	11.9[f]	NC
Chimpanzee/ Pan troglodyte	10	980309	102515 (XOMA)	2/M[h], 2/F	22.2 ± 6.29[d]	NC	132 ± 42.0[e]	8.28 ± 3.14	69.8 ± 13.1	6.66 ± 1.94[f]	NC
Chimpanzee/ Pan troglodyte	40	970609	(XOMA)	2/M	578	NC	NC	NC	NC	NC	NC
Subcutaneous Route											
Chimpanzee/ Pan Troglodyte	0.51	8758-9810[c]	102515 (XOMA)	1/M, 1/F	2.32[d]	1.25	6.11[e]	166	NC	1.30[f]	34.5
Chimpanzee/ Pan Troglodyte	0.5	8758-9810[g]	102515 (XOMA)	1/M, 1/F	1.57[d]	0.50	2.81[e]	380	NC	0.96[f]	21.8
Chimpanzee/ Pan Troglodyte	2	00-092-1046	G176H (GNE)	2/F	6.62[d]	1.50	32.4[e]	31.1	51.1	1.14	NC

Table 2.6.5.3 (cont'd)
Efalizumab Single-Dose Noncompartmental Pharmacokinetic Parameters in the Chimpanzee:
Intravenous and Subcutaneous Routes of Administration

Species/ Strain	Dose (mg/kg)	Study	Product Code (Material)	No./ Sex/ Group	C_{max} (µg/mL)	t_{max} (day)	AUC_{last} (µg · day/mL)	CL or CL/F[a] (mL/kg/day)	V_{ss} or V_z/F[b] (mL/kg)	$t_{1/2z}$ (days)	F (%)
Subcutaneous Route (cont'd)											
Chimpanzee/ Pan Troglodyte	2	00-092-1046	102646 (XOMA)	1/F	6.53[d]	1.00	23.1[e]	43.3	55.7	0.890	NC
Chimpanzee/ Pan Troglodyte	2	8758-9810[c]	102515 (XOMA)	3/M	6.42 ± 0.34[d]	0.39 ± 0.10	32.9 ± 2.88[e]	30.6 ± 2.51	NC	3.43 ± 0.31[f]	NC
Chimpanzee/ Pan Troglodyte	2	8758-9810[g]	102515 (XOMA)	3/M	5.54 ± 1.51[d]	0.98 ± 0.00	22.4 ± 3.79[e]	45.6 ± 8.52	NC	2.55 ± 0.46[f]	NC
Chimpanzee/ Pan Troglodyte	8	973409	102515 (XOMA)	1/M	6.50[d]	2.00	59.4[e]	16.9	119	6.07	47.9

F = Female.

GNE = Genentech.

M = Male.

NC = Not calculated.

[a] CL was calculated for the intravenous dose group, and CL/F was calculated for the subcutaneous dose group.

[b] V_{ss} was calculated for the intravenous dose group, and V_z/F was calculated for the subcutaneous dose group.

[c] First dose.

[d] C_{max}/Dose value reported.

[e] AUC_{last}/Dose value reports.

[f] Terminal half-life ($t_{1/2z}$) from compartmental curve fits of the linear part of the curve.

[g] Second dose.

[h] One male chimpanzee from 980309 10 mg/kg IV dose group was omitted from mean and SD calculations due to anti-drug anti-body formation.

Table 2.6.5.4
Efalizumab Multiple-Dose Toxicokinetic Parameters in the Chimpanzee: Intravenous Route of Administration

Species/Strain	Dose (mg/kg)	Study	Product Code Material	No./ Sex/ Group	C_{max} (µg/mL)	AUC_{last} (µg • day/mL)	CL (mL/kg/day)	V_{ss} (mL/kg)	$t_{1/2z}$ (days)
Chimpanzee/ Pan Troglodyte	2 mg/kg/day for 5 consecutive days	960809	102479 (XOMA)	1/M, 1/F	9.68[a]	118[b]	8.52	107	9.85[c]
Chimpanzee/ Pan Troglodyte	8 mg/kg LD on Day 1; QD 2 mg/kg for 13 days; QW 8 mg/kg for 6 months	961109	102496 (XOMA)	2/M, 1/F	NC	117 ± 9.28[d]	8.6 ± 0.71	NC	8.81 ± 0.85[c]
Chimpanzee/ Pan Troglodyte	40 mg/kg LD on Day 1; QD 10 mg/kg for 13 days; Recovery after Day 14	961109	102496 (XOMA)	1/M, 1/F	NC	108[d]	9.36	NC	8.83[c]
Chimpanzee/ Pan Troglodyte	40 mg/kg LD on Day 1; QD 10 mg/kg for 13 days; QW 40 mg/kg for 6 months	961109	102496 (XOMA)	2/M, 2/F	NC	119 ± 34.7[d]	9.02 ± 2.88	NC	11.4 ± 4.24[c]
Chimpanzee/ Pan Troglodyte	40 mg/kg/day for 2 consecutive days	970909	10249 (XOMA)	3M	1700 ± 460	NC	NC	NC	11.4 ± 4.20[c]

Key for Table 2.6.5.4

F = female; LD = Loading dose; M = Male; NC = Not calculated; QD = Every day; QW = Every week

[a] Cmax/dose was reported
[b] AUClast/dsoe was reported.
[c] Compartmental terminal half-life ($t_{1/2}\alpha$)
[d] Total AUClast/cumulative dose value reported.
[e, f] Refers to safety factors. Safety factors were not included when copying this table because the purpose of including the table in this review was to show kinetics data, not safety factor data.

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Table 2.6.5.5
muM17 Single-Dose Noncompartmental Pharmacokinetic Parameters in the Mouse:
Intravenous and Subcutaneous Route of Administration

Species/ Strain	Dose (mg/kg)	Study	No./Sex/ Timepoint	C_{max} (µg/mL)	t_{max} (day)	AUC_{last}/Dose (µg • day/mL)/ (mg/kg)	CL or CL/F[a] (mL/kg/day)	V_{ss} or V_z/F[b] (mL/kg)	$t_{1/2z}$ (days)	F (%)
Intravenous Route										
Mouse/CD-1	1	99-393-1049	3/F	18.1	NC	8.83	104	155	1.10	NC
Mouse/CD-1	3	02-224-1046	2/M	67.7	NC	83.0[c]	36.4	75.9	1.45	NC
Mouse/CD-1	3[d]	02-224-1046	2/M	63.7	NC	81.8[c]	37.2	80.6	1.50	NC
Mouse/CD-1	3[e]	02-224-1046	2/M	57.8	NC	77.0[c]	39.0	84.2	1.50	NC
Mouse/CD-1	10	99-393-1049	3/F	250	NC	67.3	14.8	102	6.28	NC
Subcutaneous Route										
Mouse/CD-1	1	99-393-1049	3/F	2.97	1	5.17	166	287	1.20	62.8
Mouse/CD-1	3	99-393B-1049	3/F	31.6	1	48.3	19.8	67.6	2.37	NC
Mouse/CD-1	3[f]	02-224-1046	2/M	12.7	1.25	59.2[c]	52.2	121	1.60	NC
Mouse/CD-1	3[g]	02-224-1046	2/M	12.2	2	58.1[c]	53.2	111	1.45	NC
Mouse/CD-1	3[h]	02-224-1046	2/M	13.8	1.25	68.6[c]	43.8	102	1.61	82.5
Mouse/CD-1	3[i]	02-224-1046	2/M	13.2	2	65.6[c]	46.2	95.1	1.43	80.1
Mouse/CD-1	3[j]	02-224-1046	2/M	14.4	1.25	67.0[c]	44.6	101	1.56	86.9
Mouse/CD-1	3[k]	02-224-1046	2/M	13.2	2	54.6[c]	56.7	115	1.41	NC

Table 2.6.5.5 (cont'd)
muM17 Single-Dose Noncompartmental Pharmacokinetic Parameters in the Mouse:
Intravenous and Subcutaneous Route of Administration

Species/ Strain	Dose (mg/kg)	Study	No./Sex/ Timepoint	C_{max} (µg/mL)	t_{max} (day)	AUC_{last}/Dose (µg • day/mL)/ (mg/kg)	CL or CL/F[a] (mL/kg/day)	V_{ss} or V_z/F[b] (mL/kg)	$t_{1/2z}$ (days)	F (%)
Subcutaneous Route										
Mouse/CD-1	5	99-393B-1049	3/F	53.7	1	64.[c]	15.2	73.9	3.36	NC
Mouse/CD-1	10	99-393-1049	3/F	67.9	2	58.8	16.6	105	4.39	88.7

F = Female; M = Male; NC = Not calculated.

[a] CL was calculated for the intravenous dose group, and CL/F was calculated for the subcutaneous dose group.

[b] V_{ss} was calculated for the intravenous dose group, and V_z/F was calculated for the subcutaneous dose group.

[c] AUC_{inf} was reported.

[d] ^{125}I-muM17 G0 + muM17 G0

[e] ^{125}I-muM17 G2 + muM17 G2

[f] muM17 (XOMA-like formulation)

[g] ^{125}I-muM17 + muM17 (GNE-like formulation)

[h] ^{125}I-muM17 + muM17

[i] ^{125}I-muM17 G0 + muM17 G0

[j] ^{125}I-muM17 G2 + muM17 G2

[k] ^{125}I-muM17 + muM17 + MHM24

Table 2.6.5.6
muM17 Multiple-Dose Toxicokinetic Parameters in the Mouse:
Subcutaneous Route of Administration

Species/ Strain	Dose (mg/kg)	Total No. Weekly Doses	Study	No./Sex/ Timepoint	Sampling Days Postdosing	Maternal Mean Concentrations (µg/mL)	Fetal Plasma (µg/mL)	Amniotic Fluid
Mouse/CD-1	3	2	00-520A-1047	4/F	Up to 7 days post 2nd weekly dose	4.80–17.0[b]	NA	NA
Mouse/CD-1	3	2	01-245-1049	6/F	5 days post 2nd weekly dose	16.9 ± 7.39	NA	NA
Mouse/CD-1	10	2	01-245-1049	6/F	5 days post 2nd weekly dose	58.6 ± 12.7	NA	NA
Mouse/CD-1	30	1 dose on Day 7	01-245-1049	6/F	4 days post 1st weekly dose	146 ± 81.0	NA	NA
Mouse/CD-1	30	2	01-245-1049	6/F	4 days post 2nd weekly dose	437 ± 116	NA	NA
Mouse/CD-1	3	3	00-319-1049	17/F	2 days post 3rd weekly dose	4.29 ± 0.98	NA	1.55 ± 0.35
Mouse/CD-1	3	4	00-297-1047	2–4/F	Up to 14 days post 4th weekly dose	2.49–16.7[b]	NA	NA
Mouse/CD-1	3	4	00-576-1049[c]	25/F	Up to 69 days post 4th weekly dose	NA	LTR	NA
Mouse/CD-1	3	4	00-576-1049	25/F	Up to 228 days post 4th weekly dose	NA	LTR	NA
Mouse/CD-1	3	4	01-006-1049	3-10/F	5 to 8 days post 4th weekly dose	4.7–10.8[b]	NA	NA

Table 2.6.5.6 (cont'd)
muM17 Multiple-Dose Toxicokinetic Parameters in the Mouse:
Subcutaneous Route of Administration

Species/ Strain	Dose (mg/kg)	Total No. Weekly Doses	Study	No./Sex/ Timepoint	Sampling Days Postdosing	Maternal Mean Concentrations (μg/mL)	Fetal Plasma (μg/mL)	Amniotic Fluid
Mouse/CD-1	3	8	01-006-1049	13/M	6 days post 8th weekly dose	56.9 ± 25.7[c]	—	—
Mouse/CD-1	10	2	00-520A1047	4/F	Up to 28 days post 2nd weekly dose	13.8-81.3[b]	—	—
Mouse/CD-1	10	3	00-319-1049	18/F	2 days post 3rd weekly dose	16.0 ± 4.65	—	2.66 ± 1.08
Mouse/CD-1	10	4	99-362-1047	16–19/F	Up to 25 days post 4th weekly dose	20.6–169[b]	—	—
Mouse/CD-1	10	4	00-576-1049[c]	25/F	Up to 61 days post 4th weekly dose	NA	LTR	—
Mouse/CD-1	10	4	00-576-1049	25/F	Up to 172 days post 4th weekly dose	NA	LTR	—
Mouse/CD-1	10	4	01-006-1049	3-6/F	5 to 8 days post 4th weekly dose	50.3–89.0[b]	—	—
Mouse/CD-1	10	8	01-006-1049	13/M	6 days post 8th weekly dose	304 ± 66.3[c]	—	—
Mouse/CD-1	30	3	00-319-1049	21/F	2 days post 3rd weekly dose	52.2 ± 36.9	—	11.3 ± 6.65
Mouse/CD-1	30	4	00-297-1047	3–46/F	Up to 76 days post 4th weekly dose	4.05–355[b]	—	—

Table 2.6.5.6 (cont'd)
muM17 Multiple-Dose Toxicokinetic Parameters in the Mouse:
Subcutaneous Route of Administration

Species/ Strain	Dose (mg/kg)	Total No. Weekly Doses	Study	No./Sex/ Timepoint	Sampling Days Postdosing	Maternal Mean Concentrations (µg/mL)	Fetal Plasma (µg/mL)	Amniotic Fluid
Mouse/CD-1	30	4	00-576-1049[d]	25/F	Up to 61 days post 4th weekly dose	—	LTR	—
Mouse/CD-1	30	4	00-576-1049	25/F	Up to 172 days post 4th weekly dose	—	LTR	—
Mouse/CD-1	30	4	01-006-1049	2-8/F	5 to 8 days post 4th weekly dose	255–283[b]	—	—
Mouse/CD-1	30	8	01-006-1049	13/M	6 days post 8th weekly dose	1300 ± 438[c]	—	—
Mouse/CD-1	50	3	00-342-1049	5/F	2 days post 3rd weekly dose	82.1 ± 40.8	79.1 ± 30.2	17.6 ± 4.85
Mouse/TSG-P53	3	2	01-319-1049	6/F	5 days post 2nd weekly dose	15.6 ± 4.16	—	—
Mouse/TSG-P53	3	4	01-229-1049	6/F	7 days post 4th weekly dose	8.27 ± 5.36	—	—
Mouse/TSG-P53	3	4	01-229-1049	6/M	7 days post 4th weekly dose	34.6 ± 8.60[c]	—	—
Mouse/TSG-P53	10	2	01-319-1049	6/F	5 days post 2nd weekly dose	105 ± 25.5	—	—
Mouse/TSG-P53	10	4	01-229-1049	6/F	7 days post 4th weekly dose	141 ± 12.7	—	—
Mouse/TSG-P53	10	4	01-229-1049	6/M	7 days post 4th weekly dose	214 ± 52.9[c]	—	—

Table 2.6.5.6 (cont'd)
muM17 Multiple-Dose Toxicokinetic Parameters in the Mouse:
Subcutaneous Route of Administration

Species/ Strain	Dose (mg/kg)	Total No. Weekly Doses	Study	No./Sex/ Timepoint	Sampling Days Postdosing	Maternal Mean Concentrations (μg/mL)	Fetal Plasma (μg/mL)	Amniotic Fluid
Mouse/TSG-P53	30	4	01-229-1049	6/F	7 days post 4th weekly dose	789 ± 287	—	—
Mouse/TSG-P53	30	4	01-229-1049	6/M	7 days post 4th weekly dose	854 ± 218[c]	—	—
Mouse/TSG-P53			01-273-1049					
Mouse/TSG-P53			01-273-1049					

Key for Table 2.6.5.6

Dash = sample not collected for the study; F = female; M = male; NA = not applicable; NC = not calculated

[a] Refers to safety factors. Safety factors were not included when copying this table because the purpose of including the table in this review was to show kinetics data, not safety factor data.

[b] Range of means reported

[c] Mean and SD of male group

[d] Pooled milk samples for 3, 10, and 30 mg/kg muM17 dose groups measured LTR (less than reportable), LTR, and 16.8 ug/mL, respectively.