

Hematology: the following parameters were analyzed at the above time points

- prothrombin time (PT) and activated partial thromboplastin time (APTT) were also analyzed as indicated above
- flow cytometric analysis of peripheral blood mononuclear cells also as indicated above (hematology for WBC)

Hematology Parameters

Total leukocyte count (WBC)
Erythrocyte count (RBC)
Hemoglobin concentration (HGB)
Hematocrit value (HCT) ^a
Mean corpuscular volume (MCV)
Mean corpuscular hemoglobin (MCH) ^a
Mean corpuscular hemoglobin concentration (MCHC) ^a
Platelet count (PLT)
Relative and absolute reticulocyte count (RTC, ARTC)
White blood cell differential
Anisocytosis (ANI)
Hyperchromasia (HYPER)
Hypochromasia (HYPO)
Macrocytosis (MACRO)
Microcytosis (MICRO)
Relative and absolute polymorphonuclear neutrophil count (PLY, APLY)
Relative and absolute lymphocyte count (LYM, ALYM)
Relative and absolute monocyte count (MNO, AMNO)
Relative and absolute eosinophil count (EOS, AEOS)
Relative and absolute basophil count (BSO, ABSO)
Relative and absolute large unstained cells count (LUC, ALUC)

^a Calculated values.

Clinical chemistry: the following parameters were analyzed as listed on the blood sample collection schedule table

Serum Chemistry Parameters

Glucose (GLU)	Calcium (CAL)	Total bilirubin (TBIL)
Urea nitrogen (BUN)	Phosphorus (PHOS)	Triglycerides (TRG)
Creatinine (CRE)	Sodium (NA)	Alanine aminotransferase (ALT)
Total protein (TPR)	Potassium (K)	Aspartate aminotransferase (AST)
Albumin (ALB)	Chloride (CL)	Alkaline phosphatase (ALK)
Globulin (GLOB) ^a	Total cholesterol (CHOL)	Gamma glutamyltransferase (GGT)
Albumin/Globulin ratio (A/G) ^a		

^a Calculated values.

Immune Antibody Response Determination: serum samples were analyzed for an immune antibody response to the administered drug as listed previously on the blood sample collection table.

Keyhole Limpet Hemocyanin (KLH) Analysis: Serum samples were analyzed for anti-KLH antibodies (ability to illicit an IgG and IgM immune response) using validated ELISA procedures as listed on the previously listed schedule table.

Lymphocyte Immunophenotyping: Blood was processed using a whole blood lysis technique. Samples were analyzed by FACS (fluorescence-activated cell sorter). The relative abundance of circulating mononuclear leukocytes was determined using flow cytometric cell surface marker analysis with the antibody combinations as described in the table.

Lymphocyte Subsets for Analysis

Antibody	Subset Evaluated
CD2/CD20	Lymphocyte Purity Estimate; Total B-lymphocytes
CD3/CD4	T-helper lymphocytes
CD3/CD8	T-cytotoxic/suppressor lymphocytes
CD3/CD14	Monocytes
CD3/CD16	NK cells
CD3/CD44	Memory T-lymphocytes
CD3/CD45A	Naïve T-lymphocytes

Urinalysis: the following parameters were analyzed prior to necropsy

Urinalysis Parameters

Macroscopic evaluations	
Microscopic evaluations	
Test Strip Analysis, including:	
Glucose	Ketones
Bilirubin	Urobilinogen
Blood	Specific Gravity
pH	Nitrites
Protein	Leukocytes

Gross pathology: A full macroscopic examination was conducted on three animals per sex per group that were euthanized on Days 92 and 183. The recovery animals (two per sex per group) were euthanized on Day 267. The comprehensive macroscopic examination included the external surface of the body, all orifices, and the cranial, thoracic, and abdominal cavities and their contents, was performed on all animals. The following organs were collected, weighed, and fixed in 10% neutral buffered formalin, except for the eyes, which were fixed in Davidson’s solution:

Organs and Tissues Examined and Collected at Necropsy

Administration Sites	Intestine, Small ^a	Salivary glands
Adrenal Glands	Duodenum	Mandibular
Aorta	Jejunum	Sciatic Nerve ^a
Bone Marrow – Sternum	Ileum	Skeletal Muscle ^a
Brain ^a	Kidneys ^a	Skin
Cerebrum	Lacrimal Gland	Mammary Region
Cerebellum	Liver ^a	Spinal Cord ^a
Brain Stem	Lungs with bronchi ^a	Cervical
Esophagus ^a	Lymph Nodes ^{a,c}	Thoracic
Eyes with Optic Nerve ^b	Axillary	Lumbar
Females	Inguinal	Spleen ^{a,c}
Cervix	Mandibular	Stomach ^a
Ovaries ^a	Mesenteric	Cardiac
Uterus ^a	Males	Fundic
Vagina	Epididymides	Pyloric
Mammary Gland ^a	Prostate Gland	Thymus ^c
Femur with articular surface	Seminal Vesicle	Thyroid Glands
Gallbladder	Testes ^a	Tongue
Heart ^a	Pancreas ^a	Tonsils ^c
Intestine, Large	Parathyroid Glands	Trachea
Cecum	Peyer's patch ^c	Urinary Bladder
Colon ^a	Pituitary Gland	
Rectum	Rib with bone marrow	Macroscopic Lesions
		Animal Identification ^d

- ^a Samples collected for immunohistochemistry.
- ^b Fixed in Davidson's Solution.
- ^c Samples collected for immunohistopathology.
- ^d Collected at necropsy to retain identification.

Organ weights: The following organs were weighed:

Organs Weighed at Necropsy

Adrenal Glands	Pituitary Gland
Brain	Prostate Gland
Heart	Spleen
Liver with gallbladder (drained)	Testes
Lung	Thymus
Kidneys	Thyroid Glands (including Parathyroid Glands)
Ovaries	

- Organ-to-bodyweight percentages and organ-to-brain-weight ratios were calculated and reported in addition to absolute organ weights.

Histopathology: all tissues were examined as listed on the table listing organs collected at necropsy (above)

- Immunohistopathology assessment of lymphoid tissues - sections (approximately 5 mm³) of the spleen, thymus, Peyer's patch, tonsil, and lymph node (axillary, mesenteric, mandibular, and inguinal) were preserved for immunohistopathologic evaluation (T and B cell distribution). The tissue sections were preserved in 10% neutral buffered formalin for approximately 48 hours and then transferred to 70% ethanol. The tissue sections were embedded in paraffin blocks. Slides were prepared and stained with hematoxylin and eosin (H&E) and for CD20 (B-cell) and CD3 (T-cell) markers.

- Immunohistochemical Detection of Test Article - tissues stored but not evaluated

Adequate Battery: yes (x), no ()—explain

Peer review: yes (), no (x)

Toxicokinetic Sampling: Serum CNTO 148 concentrations were determined using a validated ELISA method.

CNTO 148 Dosing and Blood Sample Collection Time Points

Time		Group 1 (Control, N=16)	Group 2 (25 mg/kg, N=16)	Group 3 (50 mg/kg, N=16)
Day 1 (Predose)*	Week 1	BS	BS	BS
Day 1	Week 1	Sodium Chloride SC Injection	CNTO 148 SC Injection	CNTO 148 SC Injection
Day 1 (0.25 hr)	Week 1	BS	BS	BS
Day 1 (6 hr)	Week 1	BS	BS	BS
Day 2 (24 hr)	Week 1	BS	BS	BS
Day 3 (48 hr)	Week 1	BS	BS	BS
Day 4 (Predose)	Week 1	BS	BS	BS
Day 4	Week 1	Sodium Chloride SC Injection	CNTO 148 SC Injection	CNTO 148 SC Injection
Day 4 (0.25 hr)	Week 1	BS	BS	BS
Day 8 (Predose)	Week 2	BS	BS	BS
Day 8	Week 2	Sodium Chloride SC Injection	CNTO 148 SC Injection	CNTO 148 SC Injection
Day 8 (0.25 hr)	Week 2	BS	BS	BS
Day 15 (Predose)	Week 3	BS	BS	BS
Day 15	Week 3	Sodium Chloride SC Injection	CNTO 148 SC Injection	CNTO 148 SC Injection
Day 15 (0.25 hr)	Week 3	BS	BS	BS
Day 22 (Predose)*	Week 4	BS	BS	BS
Day 22	Week 4	Sodium Chloride SC Injection	CNTO 148 SC Injection	CNTO 148 SC Injection
Day 22 (0.25 hr)	Week 4	BS	BS	BS
Day 25 (Predose)	Week 4	BS	BS	BS
Day 25	Week 4	Sodium Chloride SC Injection	CNTO 148 SC Injection	CNTO 148 SC Injection
Day 57 (Predose)	Week 9	BS	BS	BS
Day 81 (Predose)	Week 12	BS	BS	BS
Day 81	Week 12	Sodium Chloride SC Injection	CNTO 148 SC Injection	CNTO 148 SC Injection
Day 81 (0.25 hr)	Week 12	BS	BS	BS
Day 81 (6 hr)	Week 12	BS	BS	BS
Day 82 (24 hr)	Week 12	BS	BS	BS
Day 83 (48 hr)	Week 12	BS	BS	BS
Day 85 (Predose)	Week 12	BS	BS	BS
Day 86	Week 12	BS	BS	BS
Day 92 or prior to Nx (Week 14)*	Week 14	BS	BS	BS
Day 113 (Predose)*	Week 17	BS	BS	BS
Day 113	Week 17	Sodium Chloride SC Injection	CNTO 148 SC Injection	CNTO 148 SC Injection
Day 141 (Predose)*	Week 21	BS	BS	BS
Day 141	Week 21	Sodium Chloride SC Injection	CNTO 148 SC Injection	CNTO 148 SC Injection
Day 165 (Predose)	Week 24	BS	BS	BS

BS: Blood sampling;

Nx: Necropsy

*: Samples assayed for CNTO 148 in both interim analysis and final analysis

Note: Dosing time points were only listed as relevant to blood samples collected for pharmacokinetic analyses

Time		Group 1 (Control, N=16)	Group 2 (25 mg/kg, N=16)	Group 3 (50 mg/kg, N=16)
Day 165	Week 24	Sodium Chloride SC Injection	CNTO 148 SC Injection	CNTO 148 SC Injection
Day 169 (Predose)	Week 25	BS	BS	BS
Day 169	Week 25	Sodium Chloride SC Injection	CNTO 148 SC Injection	CNTO 148 SC Injection
Day 176 (Predose)	Week 26	BS	BS	BS
Day 176	Week 26	Sodium Chloride SC Injection	CNTO 148 SC Injection	CNTO 148 SC Injection
Day 179 (Predose)	Week 26	BS	BS	BS
Day 179	Week 26	Sodium Chloride SC Injection	CNTO 148 SC Injection	CNTO 148 SC Injection
Day 179 (0.25 hr)*	Week 26	BS	BS	BS
Day 179 (6 hr)	Week 26	BS	BS	BS
Day 180 (24 hr)	Week 26	BS	BS	BS
Day 181 (48 hr)	Week 26	BS	BS	BS
Day 182 (72 hr)	Week 27	BS	BS	BS
Day 190	Week 28	BS	BS	BS
Day 197	Week 29	BS	BS	BS
Day 205	Week 30	BS	BS	BS
Day 211	Week 31	BS	BS	BS
Day 218	Week 32	BS	BS	BS
Day 225	Week 33	BS	BS	BS
Day 232	Week 34	BS	BS	BS
Day 239	Week 35	BS	BS	BS
Day 246	Week 36	BS	BS	BS
Day 253	Week 37	BS	BS	BS
Day 261	Week 38	BS	BS	BS
Day 267 Prior to Nx	Week 39	BS	BS	BS

BS: Blood sampling;

Nx: Necropsy

*: Samples assayed for CNTO 148 in both interim analysis and final analysis

Note: Dosing time points were only listed as relevant to blood samples collected for pharmacokinetic analyses

Results:

Mortality: none

Clinical signs: observations were generally consistent over the dosing period with the following listed notable observations reversible during the recovery period

- Mild skin erythema at the administration site was observed with similar incidence rates in control and CNTO 148-treated animals.
- Mild skin edema at the administration site occurred in three females dosed with 25 mg/kg CNTO 148 and in two females dosed with 50 mg/kg CNTO 148. None of the controls exhibited administration site edema. All of these observations occurred as isolated incidents or as episodes of less than five days.

Physical examination: no treatment-related effects

Body weights: nothing remarkable. All animals gained weight during the study and significant body weight differences between control and treated animals were not identified. Treated males gained up to 6.6% less and females up to 2.4% less than control animals.

Food consumption: no treatment-related effects. Slightly lower intake of food by 50 mg/kg males did not result in significantly lower body weight compared to the control males.

Ophthalmoscopy: no treatment-related effects

EKG, blood pressure, and heart rate: no treatment-related effects

Hematology and coagulation parameters: no treatment-related effects

Flow cytometric analysis of peripheral blood mononuclear cells:

While CNTO 148 caused no immune cell depression as increases were identified in some of the peripheral blood mononuclear cell subtypes, there was large interanimal variability and a lack of consistency among all of the animals in the affected groups. For this reason, the description is more qualitative than quantitative in nature. For the most part, the identified changes were small in relation to normal range and/or corresponding pretreatment baseline values.

Slight increases in total lymphocytes, T-lymphocytes, T-helper lymphocytes, T-cytotoxic/suppressor lymphocytes, and naïve T-lymphocytes were identified during the dosing period with usual indications of reversal during the recovery period. Memory T-lymphocyte, NK cells, and absolute monocyte counts were not remarkable.

Most notable were B-lymphocyte counts which were reversibly, moderately increased in males and females dosed with 25 or 50 mg/kg CNTO 148 (see table prepared by the reviewer). The male responses at both doses and the 25 mg/kg females responses were ≥ 2 -fold, while the 50 mg/kg female response was only 1-fold. During the recovery period, B-lymphocyte counts decreased substantially compared to baseline, but only the 50 mg/kg female group decreased to baseline.

Dose (mg/kg)	sex	Predose average n = 8	Day 2 n = 8	Day 23 n = 8	Day 86 n = 8	Day 177 (Last dose) n = 5	Day 205 (Recovery period) n = 2	Day 261 (End) n = 2
0	male	636 \pm 206 ^a	693 \pm 251	771 \pm 341	756 \pm 207	678 \pm 302	573	714
	female	684 \pm 172	593 \pm 179	655 \pm 226	685 \pm 295	597 \pm 180	448	280 ^b
25	male	447 \pm 209	711 \pm 317	908 \pm 348	1097 \pm 360	926 \pm 318	537	530 ^b
	female	409 \pm 195	578 \pm 186	731 \pm 326	819 \pm 228	784 \pm 343	807	600
50	male	551 \pm 339	1259 \pm 519	1017 \pm 693	1555 \pm 808	1107 \pm 819	744	680
	female	487 \pm 149	760 \pm 250	813 \pm 181	971 \pm 272	900 \pm 53	743	532

a – Standard deviation

b – n = 1

Clinical chemistry: no treatment-related effects

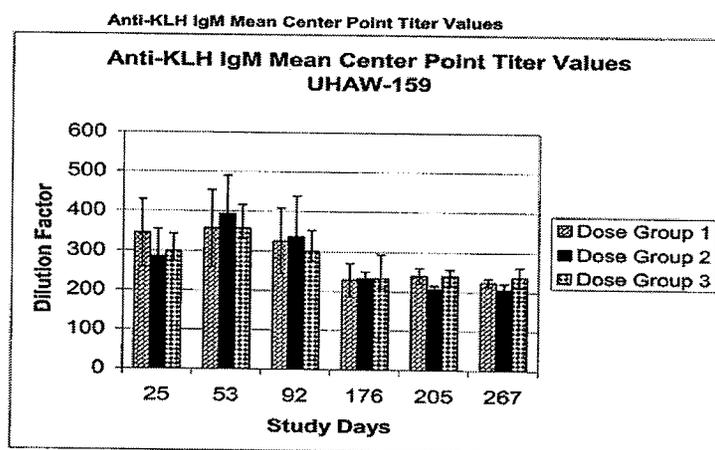
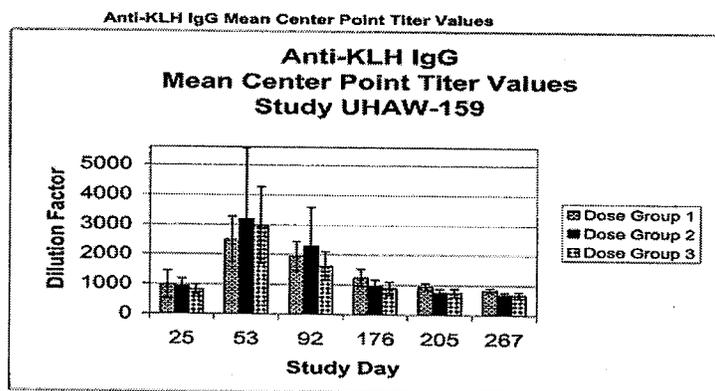
Immune Antibody Response Determination: 1 female in the low dose group exhibited an antibody response to the administered drug, while other response analysis may have been confounded (assay interference) due to the high serum concentrations of the drug.

- Antibodies to CNTO 148 were not detected in 31 of 32 animals treated twice weekly with 25 or 50 mg/kg CNTO 148 for 13 weeks or in the 16 control animals.
 - Antibodies to CNTO 148 were detected in one female dosed with 25 mg/kg CNTO 148. A competitive binding test confirmed that the immune response was specific for CNTO 148.
 - Antibodies to CNTO 148 were not detected in the remaining animals dosed twice weekly with 25 or 50 mg/kg CNTO 148 for 26 weeks. The CNTO 148-treated animals were characterized as having an inconclusive anti-product antibody response because detection of an antibody response may have been compromised by high serum levels of CNTO 148.
 - Therefore, a spike recovery test was performed to discriminate between negative and inconclusive antibody results. The positive control antibody at 50 ng/mL was added to ten-fold diluted serum from Day 1 (obtained prior to first administration), as well as sera obtained immediately preceding scheduled euthanasia (Day 92, Day 182, and Day 267). Then the immune response assay was performed as before, and the percent recovery of the known positive signal was calculated. The positive antibody spike was readily detected in Day 1 sera (range of 73.1 to 100.9%), but was no longer recovered after animals were administered 25 mg/kg and 50 mg/kg CNTO 148.
 - Use of the low 50 ng/mL concentration of positive antibody sets a very strict recovery criterion, because the assay should detect antibody to CNTO 148 when present at concentrations exceeding those of CNTO 148. Monkeys administered CNTO 148 had detectable serum CNTO 148 (>78 ng/mL) at the end of the recovery period, however, had there been substantial immune responses it should have been possible to detect them in many animals as serum concentrations of CNTO 148 declined. Therefore, although immune response results were deemed inconclusive due to detectable concentrations of serum CNTO 148, the assay should have been capable of detecting a substantial immune response, such as was observed in the on 25 mg/kg female, had such a response occurred.

Keyhole Limpet Hemocyanin (KLH) Analysis: CNTO 148 did not appear to limit/alter a monkey's ability to have a humoral response

- Administration of 25 or 50 mg/kg CNTO 148 for 13 weeks did not affect the

humoral response (i.e., anti-KLH IgG and anti-KLH IgM measured on Days 25, 53, 92, 176, 205, & 267) to intramuscular injections of 100 mcg keyhole limpet hemocyanin (KLH) in incomplete Freund's adjuvant on Days 12 and 30. Dosing in following tables for IgG and IgM responses is at 0, 25, & 50 mg/kg for Dose Group 1, 2, & 3, respectively.



Urinalysis: no treatment-related effects

Gross pathology: no treatment-related effects

Organ weights: no treatment-related effects associated with macroscopic or microscopic findings

Histopathology: twice-weekly administration of 25 or 50 mg/kg CNTO 148 for 26 weeks was associated with microscopic alterations of the administration sites but no systemic toxicity. Minimal or mild chronic, perivascular, subcutaneous inflammation was observed in at least one of the administration sites from all CNTO 148-treated males and females. Reversal of effects was observed during the recovery period. In addition, no histomorphologic findings in the lymphoid

tissues that were attributed to CNTO 148 as well as any CNTO 148-related lymphocyte subset changes were observed.

Toxicokinetics:

Thirty-one of thirty-two animals received extensive exposure to CNTO 148 throughout the six-month dosing period. One female dosed with 25 mg/kg CNTO 148 did not have measurable CNTO 148 levels in serum after Day 25. The lack of quantifiable CNTO 148 in the serum of this animal was attributed to an antibody response to CNTO 148 that was detected after Day 22. Two males who exhibited clearance profiles that were dissimilar to others dosed with 50 mg/kg CNTO 148, while exhibiting lower concentrations than in other 50 mg/kg animals, still received significant exposure to CNTO 148. In both animals, antibodies to CNTO 148 were not detected. However, as noted previously, CNTO 148 is known to interfere in the immune response assay.

In summary, CNTO 148 exposure increased in a dose proportional manner over the dose range of 25 to 50 mg/kg. A 2-fold increase in dose resulted in an approximately 1.8 to 2.2-fold increase in the observed mean trough serum CNTO 148 concentrations. The overall mean terminal half-life from both dose groups after twice weekly SC injections of CNTO 148 for up to 6 months in cynomolgus monkeys was estimated to be approximately 14 to 16 days. The average accumulation ratios calculated from the AUCs of the first to last injection were approximately 5.71 and 8.90 for the 25 mg/kg and 50 mg/kg dose groups, respectively. Mean, gender combined terminal AUC values were 2622 and 5657 $\mu\text{g}\cdot\text{day}/\text{mL}$ and C_{max} values were 1119 and 2459 $\mu\text{g}/\text{mL}$ for the 25 and 50 mg/kg groups, respectively, at the end of the study period.

Individual and Mean t1/2 Values and AUC Accumulation Ratios Following Multiple 25 or 50 mg/kg SC Injections Twice Weekly in Cynomolgus Monkeys for up to 6 months with a 12 week recovery period

Animal ID	Dose (mg/kg)	t1/2 (day)	AUC(t1-t2), t1 = Day 1; t2 = Day 4 ($\mu\text{g}\cdot\text{day}/\text{mL}$)	AUC(t1-t2), t1 = Day 179; t2 = Day 182 ($\mu\text{g}\cdot\text{day}/\text{mL}$)	Accumulation Ratio R (AUC(t1-t2))
2005	25	25.93	419.38	2726.04	6.50
2007	25	11.37	0.00	2071.25	NA
2107	25	16.62	541.93	3156.19	5.82
2108	25	11.30	526.37	2532.94	4.81
Mean (\pm SD)		16.31 (\pm 6.88)	371.92 (\pm 253.86)	2621.60 (\pm 449.98)	5.71 (\pm 0.85)
3002	50	14.36	770.15	3612.25	4.69
3007	50	14.50	0.00	5364.66	NA
3107	50	16.32	513.49	8653.32	16.85
3108	50	12.07	969.62	4999.59	5.16
Mean (\pm SD)		14.31 (\pm 1.74)	563.32 (\pm 419.39)	5657.46 (\pm 2135.15)	8.90 (\pm 6.89)

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 Six month IV mouse study with cVq1 analogous anti-mouse TNF α mAb: see 2.6.6.1 - Overall Toxicology Summary for study summary

2.6.6.4 Genetic toxicology - Not Applicable (see 2.6.6.1 - Overall Toxicology Summary)

2.6.6.5 Carcinogenicity - Not Applicable (see 2.6.6.1 - Overall Toxicology Summary)

2.6.6.6 Reproductive and developmental toxicology

Fertility and Early Embryonic Development

Mouse: no studies were conducted with golimumab (see 2.6.6.1 - Overall Toxicology Summary for mouse fertility studies using cV1q, an analogous anti-mouse TNF α mAb originally submitted with the Centocor BLA 103,772)

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Embryofetal Development

Mouse: see 2.6.6.1 - Overall Toxicology Summary for mouse embryofetal studies using cV1q, an analogous anti-mouse TNF α mAb originally submitted with the Centocor BLA 103,772

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Study title: A Study for the Effect of CNTO 148 on Embryo-Fetal Development in Cynomolgus Monkeys by Twice Weekly Subcutaneous Administration

Key study findings:

- Pregnant female Cynomolgus monkeys were doses by the subcutaneous route 2x weekly from days 20 to 51 of gestation at doses of 0, 25, or 50 mg/kg CNTO 148.
- High dose group dams gained 8% less weight than controls while low dose dams gained comparable weight as controls
- Anti-product antibody production was characterized as being an inconclusive because the lack of detection of an antibody response in all but 1 low dose female may have been compromised by high serum levels of CNTO 148 in the detection assay.
- The immunohistochemical evaluation for anti-CD20+, anti-CD3+ and anti-CD34+ immunoreactivity of spleen, thymus and mesenteric lymph node tissue sections in the fetuses did not reveal any golimumab effects on the B and T lymphocytes and hematopoietic stem cells
- Fetal blood levels detected at cesarean section were variable and the fetal:maternal ratios ranged from 0.25-0.56 (mean of 0.38) at 25 mg/kg and from 0.51-3.61 (mean of 1.32) at 50 mg/kg. At this time, maternal levels were 3-5% of what they were after the last dosing day 51
- The No Observed Adverse Effect Level was 50 mg/kg/day for both pregnant cynomolgus monkeys and for embryo-fetal development with an associated TK

values of 27,051 $\mu\text{g}\cdot\text{day}/\text{mL}$ (AUC) and 1,613 mcg/mL (Cmax) in the maternal animals with a half-life of 11 days.

Study no.: _____ Study Number: _____ .050.04, Centocor Study Number: T-2003-005

Volume #, and page #: cCTD

Conducting laboratory and location: _____

b(4)

Date of study initiation: March 26, 2003 (report date April 4, 2004)

GLP compliance: yes

QA reports: yes (x) no ()

Drug, lot #, and % purity: CNTO 148 (human tumor necrosis factor α [TNF α] monoclonal antibody [mAb]), lot 5873:122, 99.0% purity

Methods

Doses: 0 (0.9% saline), 25, & 50 mg/kg

- stability and concentration of the formulated test article was conducted by the sponsor and were within acceptable limits

Species/strain: Cynomolgus monkeys

- pre-study age (4.3-8.3 years - females, 5.9-8.6 years - males)

- pre-study weight (2.84-6.70 kg – females, 7.10-10.82 kg – males)

Number/sex/group: pregnant females - 12 for 0 & 25 mg/kg groups, 14 for 50 mg/kg group

Route, formulation, volume, and infusion rate: subcutaneous (intrascapular area), aqueous, 0.5 mL/kg (0 & 50 mg/kg groups) and 0.25 mL/kg (25 mg/kg group), single bolus dose

Dosing: 2x weekly from days 20 to 51 of gestation (dosed on Days 20, 23, 27, 30, 34, 37, 41, 44, 48 and 51 of gestation, for a total of 10 doses per animal) or until abortion confirmed.

Satellite groups used for toxicokinetics: all study animals used

Study design:

Mating - Females were mated with males for three consecutive days on a one-to-one basis (middle of session is day 0 of gestation, GD 0). This three-day mating session took place between Day 11 and Day 15 of menstruation (the first day of onset of menstruation = Day 1 of menstruation). Once pregnancy was confirmed, the females were randomly assigned to a study group on that day.

Clinical signs:

- observations - on dosing days (GDs 20, 23, 27, 30, 34, 37, 41, 44, 48 and 51), full observations were performed on all dams prior to dosing and approximately two to three hours after dosing, and mortality was checked a minimum of four hours after the initial clinical observations. On non-dosing days including acclimation and the day of scheduled cesarean section, full observations were performed in the morning and mortality was checked a minimum of four hours after the initial clinical observations.

- Pregnancy monitoring - Embryonic/fetal viability was monitored by ultrasound under sedation with 5 to 20 mg/kg ketamine (IM, with supplemental 5 to 10 mg/kg ketamine as necessary) on GDs 25, 30, 37, 44, 51, 60, 70, 80 and 90 (\pm 1 day)
- Monkey chorionic gonadotropin (mCG) assay - confirm that the high dose animals diagnosed as having aborted by GD25 were pregnant at the time of dosing on GD20 and GD23, monkey chorionic gonadotropin (mCG, active form) was measured on select dams using back-up serum from toxicokinetic samples
- Body weights: GDs 1 (at the end of the three-day mating session), 19, 26, 33, 40, 47, 54, 61, 68, 75, 82, 89 and 100 (\pm 1 day)
- Food consumption: biscuit count daily until day before scheduled cesarean section except for 3-day mating period
- Immunological examinations of dams and fetuses: blood was collected once on GDs 18-20 (pre-dose), 35 (approximately 24 hours after the 5th dose), 52 (approximately 24 hours after the last dose), and on the day of cesarean section (before sedation and anesthesia). Fetal cord blood was collected from the umbilical vein from even-numbered dams during the cesarean section
- analysis of differential leukocyte counts and flow cytometry analyses for absolute counts and percentages of CD3+ (T-lymphocytes), CD3+CD4+ (T-helper lymphocytes), CD3+CD8+ (T-cytotoxic suppressor lymphocytes), CD20+ (B lymphocytes), and CD45+ cells
- TK and immune response antibodies in dams and fetuses determinations: blood was collected once at pre-dose on GDs 18-20, 23 and 51, approximately 24 hours after administration on GDs 20 and 51, once in the morning on GDs 54, 58, 72 and 86, and on the day of cesarean section (before sedation and anesthesia). Fetal cord blood was collected from the umbilical vein from odd-numbered fetuses during the cesarean section.
- Gross necropsy:
- dams - none on dams as no mortality or moribund sacrifices
- Fetal exams:
- Harvest - pregnancies were terminated between GD 100 and GD103 by cesarean section, and each fetus was subjected to a teratological evaluation
- all amniotic fluid was collected for volume measurement
- Fetal viability, external examinations, and fetal and placental weights
- Measurements:
- Head width, distance between the eyes, head circumference, chest circumference, crown-rump length, tail length, paw and foot length (right), anogenital distance, amniotic fluid volume, diameters of primary and secondary placenta

Observations:

Body form, symmetry of head, facial form, mandibular formation, eyes and eyelids, hair of head, nipple formation, anus, fingers, toes, finger and toe nails, ears, tail, upper and lower extremities, external genitalia, vertebral column, umbilical cord and palate.

Fetal visceral examinations and organ weights

- each surviving fetus for macroscopic observations of organs and tissues
- following organs weighed and fixed in 10% neutral buffered formalin (NBF):
 - adrenal glands, testes, ovaries, heart, lungs, spleen, thymus, liver, kidneys, uterus, brain and mesenteric lymph node
 - after adequate fixation, the spleen, thymus and mesenteric lymph node trimmed and processed for standard paraffin embedding and sectioning for fetal tissue immunohistochemistry
- following organs were fixed in 10% NBF without weighing:
 - eyes, stomach, small and large intestines, the skin of the head, ears, trachea (with thyroids), esophagus, aorta, tongue, epididymides, prostate/seminal vesicle, urinary bladder, and any abnormal organs/tissues noted during the gross observation

Fetal skeletal examination

- the carcass of each surviving fetus was fixed in ethyl alcohol, and skeleton was stained by Dawson's method

Parameters and endpoints evaluated:

- relative organ weights were calculated as percentages of final body weight and brain weight.
- Dams: food consumption (biscuit counts), body weight, differential leukocyte counts, immunophenotyping analyses by flow cytometry, abortion/embryo-fetal death ratio
- Fetus: Fetal weight, placental weight, external measurements, organ Weight (absolute and relative weights), skeletal development (number of bones with ossification centers of the vertebral centrum, skeletal length (right side of ossified parts of the humerus, ulna, radius, femur, tibia) and fibula), differential leukocyte counts, immunophenotyping analyses by flow cytometry, incidences of external and placental abnormalities, visceral abnormalities and variations, and skeletal abnormalities and variations

Results

Mortality (dams): no maternal deaths or moribund sacrifices

Clinical signs (dams): no treatment-related effects

- Abortions - control: 1 of 12 control (GD30)
 - high dose group: 4 of 14 before dosing started (pre-GD20)
 - confirmed by monkey Chorionic Gonadotropin (mCG) assay

Body weight (dams): no treatment-related effects (see table) except that the high dose group did not gain as much weight (10%) compared to control (18%) from GD1 until C-section

- all groups lost weight during the course of the dosing period (GD20-51)
 - -5%, -4%, & -8% of body weight for control, low dose and high dose, respectively
- all groups gained weight immediately after dosing ended (GD47 until C-section)
 - +16%, +17%, & +15% of body weight for control, low dose and high dose, respectively
- all groups gained weight from GD1 until C-section (see reviewer created table for mean values)
 - +18%, +19%, & +10% of body weight for control, low dose and high dose, respectively

Mean ± SD for body weight measurements in kg in pregnant Cynomolgus monkeys treated biweekly with golimumab GD20-51					
Dose (mg/kg)	GD1	GD19	GD47	GD54	GD100+ (C-section)
0	4.32±0.89	4.49±0.94	4.28±0.96	4.38±0.96	5.09±1.01
25	4.44±1.00	4.57±0.97	4.41±0.99	4.52±1.02	5.27±0.99
50	4.69±0.89	4.72±0.86	4.36±0.87	4.49±0.93	5.18±0.90

Food consumption (dams): no treatment-related effects

Immunological examinations of differential leukocyte counts and flow cytometry analyses (lymphocytes): no treatment-related effects in dams and fetuses

Toxicokinetics:

Exposure to golimumab was observed in both the maternal and feral circulation. Exposure, as assessed by the Cmax and AUC values, increased with dose over the dose range of 25 to 50 mg/kg. A 2-fold increase in dose from 25 to 50 mg/kg resulted in an approximately 2.5 & 2.7-fold increase in Cmax and AUC values after the last dose, respectively. Fetal/maternal ratios no days 100-103, ~4 half-lives after the last maternal dose and a blood levels of 3-5% observed after the last

dose, were 0.38 for the 25 mg/kg groups and 1.32. For the 50 mg/kg group, ratio values for the 4 fetal animals were 0.51, 0.57, 0.59, & 3.61, suggesting that fetal/maternal ratio was more likely to be ~0.5. Actual fetal values after the last dose were not determined. (see reviewer created table for mean values)

Mean ± SD for TK measurements following last day of dosing (GD51) with Golimumab in Pregnant Cynomolgus Monkeys and the Day 100-103 Fetal/Maternal Ratio					
Dosing Period (GD20-51)					C-section GD100-103
Dose (mg/kg)	Cmax (mcg/mL)	Tmax (day)	AUC (µg•day/mL)	t1/2 (day)	Fetal/maternal ratio
25	656±150	52.0±52.5	10,025±2,771	12±9.8	0.38±0.13
50	1613±300	52.0±52.5	27,051±7,105	11.3±10.2	1.32±1.53 ^a

a – ratio values for the 4 fetal animals were 0.51, 0.57, 0.59, & 3.61, suggesting that fetal/maternal ratio 50 days after the last dose was more likely to be ~0.5

Immune response antibodies: Antibodies to golimumab were detected in only one animal in the day 100 maternal serum from one monkey in the low dose group. This monkey had the second most rapid elimination of golimumab and had a serum concentration below the lower limit of quantification at the time of cesarean section.

While no other immune responses were detected in dams or fetuses, because the presence of golimumab in an immune response sample may hinder detection of the immune response, these results were characterized as being inconclusive or negative based upon the respective presence or absence of detectable serum golimumab. This situation is the same as described in the chronic monkey study.

Terminal and necroscopic evaluations:

Nothing remarkable was observed for external fetal examinations that included viability, weight, placental weight, head width, distance between the eyes, head circumference, crown-rump length, tail length, chest circumference, anogenital distance, paw length, foot length, primary and secondary placental diameter, and amniotic fluid volume.

Nothing remarkable was observed for fetal visceral examinations, organ weights (absolute and relative), and skeletal examinations.

The immunohistochemical evaluation for anti-CD20+, anti-CD3+ and anti-CD34+ immunoreactivity of spleen, thymus and mesenteric lymph node tissue sections did not reveal any golimumab effects on the B and T lymphocyte and hematopoietic stem cell populations of these tissues.

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Prenatal and Postnatal Development

Mouse: see 2.6.6.1 - Overall Toxicology Summary for mouse peri/post-natal studies using cV1q, an analogous anti-mouse TNF α mAb originally submitted with the Centocor BLA 103,772)

Study title: A Study for the Effect of CNTO 148 on Pre- and Postnatal Development, including Maternal Function in Cynomolgus Monkeys by Twice Weekly Subcutaneous Administration

Key study findings:

- Pregnant female Cynomolgus monkeys were doses by the subcutaneous route 2x weekly from day 50 of gestation to day 33 after delivery at doses of 0, 25, or 50 mg/kg CNTO 148.
- Nothing remarkable noted for maternal animals or neonates.
- The immunological and immunohistochemical evaluations did not reveal any treatment-related effects on antibody production, the B and T lymphocytes and hematopoietic stem cells, and associated organs. Anti-product antibody production was characterized as being inconclusive because the lack of detection of an antibody response may have been compromised by high serum levels of CNTO 148
- The No Observed Adverse Effect Level was 50 mg/kg/day for both pregnant cynomolgus monkeys and neonatal development associated with maternal C_{max} values of 1,482 μ g/mL and highest neonate blood levels of 537 mcg/mL. Maternal milk levels were 3.6 μ g/mL at 50 mg/kg. Up to 36% of maternal blood levels were measured in the neonate blood.

Study no.: Study Number: 27-14, Centocor Study Number: T-2004-007

Volume #, and page #: eCTD

Conducting laboratory and location:

b(4)

Date of study initiation: July 15, 2004 (final report November 1, 2007)

GLP compliance: yes

QA reports: yes (x) no ()

Drug, lot #, and % purity: CNTO148, D03PA7222 & DO3PG7263, purity 99.2% and 98.9%, respectively

- stability results are within the protocol specifications

Methods

Species/strain: Cynomolgus monkeys (*Macaca fascicularis*)

- females: age 3-10 years old; weight 2.50-4.48 kg on day 0 of gestation

- mating males: age \geq 5 years old

Doses employed: 0 (0.9% saline), 25, & 50 mg/kg

Number/sex/group: 12 mated females/group

- females referred to as dams in the report (Japanese translation?)

Route of administration: subcutaneous

Dosing: 2x weekly from day 50 of gestation to day 33 after delivery

- dose volume 0.25 mL/kg (25 mg/kg dose) and 0.5 mL/kg (50 mg/kg dose)

- dose to shaved back

Satellite groups used for toxicokinetics: none (all study animals for TK)

Study design:

Mating and confirmation of pregnancy:

- 3 day mating period (12th-14th days of menstrual cycle) for regular menstrual females with proven males

- middle of mating period is Day 0 of gestation (GD0)

- day of delivery day) of lactation (LD0)

- confirmation of pregnancy on GD25 and 49 by ultrasound

- fetal viability confirmed on GD25, 49, 60, 70, 80, 90, 100, 120, & 140

Clinical signs:

- 1x daily (non-dosing period), 2x daily (dosing period)

- nursing observed daily until day 180 of lactation

Body weights and Food Consumption:

- Days 0, 20, 25, 40, 50, 60, 70, 80, 90, 100, 120, 140 & 150 of gestation

- Days 1, 8, 14, 21, 28, 35,42,49, 60,70, 80 & 90 of lactation.

Clinical Pathology:

Hematology and Serum Biochemistry:

- Dams: GD49 (pretreatment) & 149,

- F1: LD28, 58, & 178

TK and immune response determinations:

Blood Sampling Point	Blood Sampling Volume (mL)	Volume and No. of Serum Aliquots	Number of Serum Sample Shipments	
			1st Set	2nd Set
Prior to Dose 1 (Day 50)	1.8	0.25 mL × 3	TK, IR	BU
24 hr post Dose 1 (Day 51)	1.2	0.25 mL × 2	TK	BU
Prior to Dose 2 (Day 54)	1.2	0.25 mL × 2	TK	BU
Prior to Dose 5 (Day 64)	1.2	0.25 mL × 2	TK	BU
Prior to Dose 8 (Day 75)	1.8	0.25 mL × 3	TK, IR	BU
Prior to Dose 16 (Day 103)	1.8	0.25 mL × 3	TK, IR	BU
Prior to Dose 24 (Day 131)	1.2	0.25 mL × 2	TK	BU
Prior to Dose 28 (Day 145)	1.8	0.25 mL × 3	TK, IR	BU
Prior to Dose 10 (last dose) after delivery (Day 33 after delivery)	1.8	0.25 mL × 3	TK, IR	BU

Day 34 after delivery (1 day after last dose)	1.2	0.25 mL × 2	TK	BU
Day 60 after delivery	1.8	0.25 mL × 3	TK, IR	BU
Day 90 after delivery	1.2	0.25 mL × 2	TK	BU
Day 120 after delivery	1.8	0.25 mL × 3	TK, IR	BU
Day 180 after delivery	1.8	0.25 mL × 3	TK, IR	BU

TK = Toxicokinetics sample for CNTO 148 serum concentrations

IR = Immune response sample for determination of anti-CNTO 148 antibodies

BU = Backup sample

Day = Day of gestation

Milk Analysis:

- Milk samples (approximately 1 mL from each animal) were collected from all dams in all groups once on Days 14 and 28 of lactation, and 2 days after dosing

Gross necropsy:

- one (1) 50 mg/kg dam with F1 death with full tissue complement fixed in formalin but not evaluated
- all other dams survived and were returned to the breeding colony

Fetal exams:

Observations at birth - Each F1 animal was examined for viability, sex and external malformation. Dead, but intact F1 animals found at birth were necropsied and examined for abnormalities. The brain, eyes, stomach, small intestine, large intestine, skin of head, ears, thymus, heart, lungs, spleen, liver, kidneys, adrenal glands, testes or ovaries and uterus, placenta (where possible) and carcass were fixed in 10 vol% neutral buffered formalin and stored

Clinical Signs - All F1 animals were observed twice daily during the lactation period (through Day 90 after birth) and once daily after the weaning period (from approximately Day 91 until Day 180 after birth).

Body Weight - All F1 animals were weighed on Days 1, 7, 14, 21, 28, 35, 42, 50, 60, 70, 80, 90, 100, 110, 130, 150 and 180 after birth.

Clinical Pathology - Blood samples for hematology and serum biochemistry were collected from F1 animals on Days 28, 58 and 178 after birth.

Immunological Examinations - Blood samples for immunological examinations (Lymphocytes CD3, CD4, CD8, & CD20) were drawn from the femoral vein (all F1 animals) on Days

62, 92 and 180 after birth

Functional Development Examinations until Weaning - Pupil reflex, Preyer reflex, pain reflex and grip strength were evaluated in all F1 animals on Day 35 after birth.

Functional Development Examinations between Day 150 and Day 170 after Birth – 1 ophthalmic exam and 1 ECG exam

Morphological Development - measured for all F1 animals on Days 30, 90 and 180 after birth: head width, distance between the eyes, crown-rump length, tail length, chest circumference, paw and foot length, anogenital distance.

Immunological Development - Humoral immune competence by Antibody response to KLH and tetanus toxoid and cellular Immune competence by delayed-type hypersensitivity reaction were examined (all F1 animals) between Day 120 and Day 180 after birth.

Toxicokinetics and Immune Response

Blood Sampling Point	Blood Sampling Volume (mL)	Volume and No. of Serum Aliquots	Serum Samples for Shipment
Day 15 after birth	1.2	0.25 mL × 2	TK, IR
Day 30 after birth	1.2	0.25 mL × 2	TK, IR
Day 60 after birth	1.2	0.25 mL × 2	TK, IR
Day 120 after birth	1.2	0.25 mL × 2	TK, IR
Day 180 after birth	1.2	0.25 mL × 2	TK, IR

TK = Toxicokinetics sample for CNTO 148 serum concentrations

IR = Immune response sample for determination of anti-CNTO 148 antibodies

Gross Pathological Examinations - F1 animals that died were necropsied as soon as possible following death, and examined macroscopically. Surviving F1 animals were necropsied and examined macroscopically on Day 180 after birth (six F1 animals per treatment group) or, in the additional necropsy, between Day 209 and Day 235 after birth (all remaining F1 animals).

- tissue processing: the organs and tissues stated below (see table) were fixed as follows: the eyeballs and optic nerves in a mixed solution of formaldehyde and glutaraldehyde, the testes in Bouin's solution, and all other organs in 10 vol% neutral buffered formalin (except for the brain, thymus, heart, lungs, spleen, liver, kidneys, adrenal glands, testes, eyes, stomach, small intestine, large intestine, skin of

head, ears and carcass were fixed in 10 vol% neutral buffered formalin)

Adrenal glands ^{a)}	Aorta (thorax)	Bone (femur, sternum)	Bone marrow (left femur)
Brain (cerebrum, cerebellum, pons, medulla oblongata)	Diaphragm	Epididymides ^{a)}	Esophagus
Eyeballs, with optic nerves ^{a)}	Gall bladder	-	Heart
Urinary bladder	Intestine (duodenum, jejunum, ileum, including Peyer's patches, cecum, colon, rectum)	Kidneys ^{a)}	Liver
Lungs, ^{a)} with bronchi	Lymph nodes (submandibular ^{a)} and mesenteric)	Mammary glands ^{a)} (only females)	Ovaries ^{a)}
Pancreas	Pituitary	Prostate	Sciatic nerve
Seminal vesicles ^{a)}	Skeletal muscle ^{a)} (quadriceps femoris)	Skin ^{a)} (pectoral region)	Spinal cord (thorax)
Spleen	Stomach	Submandibular glands ^{a)}	Testes ^{a)}
Thymus	Thyroids, ^{a)} with parathyroids	Tongue	Trachea
Uterus	Vagina	Tetanus toxoid injection site	-

a) Both left and right organs/tissues were collected

Histopathological Examinations - The organs and tissues stated below for the six F1 animals per treatment group sacrificed on Day 180 after birth were examined histopathologically by standard H. and E. staining.

Adrenal glands ^{a)}	Brain (cerebrum; diencephalon, parietal lobe, temporal lobe; cerebellum, pons, medulla oblongata)	Bone marrow (left femur)	Heart
Kidneys ^{a)}	Liver	Lungs ^{a)}	-
Ovaries ^{a)}	Spleen	Testes ^{a)}	Thymus
Uterus	Lymph nodes (mesenteric and submandibular ^{a)})	Peyer's patches (ileum)	-

a) Both left and right organs were examined

- At the additional necropsy, the organs and tissues stated below of F1 animals were examined histopathologically by standard H. and E. staining.

Liver	Spleen	Bone marrow (left femur)	Thymus
-	Lymph nodes (mesenteric and submandibular ^{a)})	Peyer's patches (ileum)	-

a) Both left and right organs were examined

Immunological examinations were conducted in the six F1 animals sacrificed on Day 180 after birth from each

group by immunohistochemical staining and standard H. and E. staining of bone marrow, thymus, spleen, Peyer's patches and lymph nodes. T cell (CD3) and B cell (CD20) distribution in the immunohistochemically stained organs and tissues were examined. Immunological examinations were not conducted for the F1 animals at the additional necropsy.

Results

F₀ in-life:

- no mortality or clinical signs
- fetus/neonate events not remarkable
- stillbirth percentages were 16.7% (2/12), 0.0% (0/12) and 25.0% (3/12) in the control, 25 and 50 mg/kg groups, respectively, and not considered remarkable as historical control of 21.3% F1 loss)
 - control (abortion GD117, stillbirth DG160, premature delivery/stillbirth GD130
 - 25 mg/kg (death GD140/LD1 – stillbirth?)
 - 50 mg/kg (3 stillbirth GD150, 159, & 163; death GD158/LD11)
- nothing remarkable for body weight, food consumption, hematology, and serum biochemistry

Toxicokinetics (maternal blood, milk and neonate):

- dose proportional C_{max} for 25 and 50 mg/kg dose at 1.82-fold and 1.74-fold after the first dose (GD50) and last dose (LD33), respectively
- mean C_{max} accumulation ratio, from last dose to that of the initial dose, was 4.8 and 4.6 in the 25 and 50 mg/kg groups, respectively
- mean half-life values in dams were estimated to be 16.61 and 29.47 days in the 25 and 50 mg/kg groups, respectively
 - no difference in neonates relative to dams
- drug detected in the milk on Days 14 and 28 of lactation with the mean values of 0.75 and 0.79 µg/mL in the 25 mg/kg group and 3.65 and 3.62 µg/mL in the 50 mg/kg group.
- on ~LD30 fetal:maternal ratios were 0.16 and 0.18 for the 25 and 50 mg/kg dose groups, respectively

Summary of maternal and neonatal serum exposure levels ($\mu\text{g/mL}$) following treatment of pregnant macaques from Day 50 of gestation through Day 33 of lactation

Dose (mg/kg)	Maternal Serum				Breast Milk	Neonatal Serum		
	C _{max} First Dose (GD51)	C _{max} Last Dose (LD34)	27-days After Last Dose (LD60)	6-Month After Delivery (Day 180)	LD28	15-Days After Birth (LD15)	30-Days After Birth (LD30)	6-Months After Birth (Day 180)
25	176 \pm 100	851 \pm 355	214 \pm 79	4.7 \pm 5.7	0.79 \pm 0.19	219 \pm 99	140 \pm 49	1.2 \pm 0.9
50	321 \pm 256	1482 \pm 813	387 \pm 259	9.3 \pm 6.9	3.6 \pm 2.1	537 \pm 221	274 \pm 124	3.2 \pm 2.4

GD = Gestation Day

LD= Lactation Day

Immune response (anti-product antibody):

- 3 of 12 controls, 5 of 12 low dose treated females, and 0 of 12 high dose Females were positive for antibodies to CNTO 148
- low titers (≤ 80) in all but 1 low dose female (highest titer of 2560) which exhibited accelerated clearance
 - neonate antibody titer of 160 but no drug levels
- presence of anti-product antibody in 3 of 12 control dams was investigated by the sponsor, but they were not able to explain it
- 19 treated females were inconclusive (7 low dose and 12 high dose)
- 1 of 5 treated positive females in the 25 mg/kg group exhibited accelerated clearance
- Drug antibody production was characterized as being an inconclusive immune response because the lack of detection of an antibody response may have been compromised by high serum levels of CNTO 148 as was observed in other monkey studies

F₀ necropsy: Erosion/ulceration and induration in the bilateral papillary areas, external and subcutaneous (mammary, dosing site, other?), were noted in the 50 mg/kg maternal animal whose neonate died GD158/LD11 that was necropsied. Toxicological relevance unknown.

F₁ physical development:

- no morphological abnormalities in dead or live fetuses/neonates
- one F1 in the 25 & 50 mg/kg group died on Day 1 and Day 11 after birth, respectively.
 - these F1s exhibited lower body weight (281 g vs. control mean of 342 g and 234 g versus control mean of 365 g on day 7, respectively), and there was no content in the stomach of the 25 mg/kg F1 animal
- nothing else remarkable for body weights
- nothing remarkable for hematology and serum biochemistry
 - in the 50 mg/kg group, a 47% increase in neutrophilic leukocyte (%) and a 13% decrease in lymphocyte (%) were noted on Day 178 after birth when compared with the control group. However, these were not considered of toxicological relevance because no abnormalities

- were noted in the absolute counts or other hematological parameters
- in the 25 mg/kg and 50 mg/kg groups, a 21% increase in total cholesterol compared to control was observed on Day 58 after birth with the values being -9% and 11% on Day 178, respectively. Observations not considered toxicologically relevant as relatively small changes with no dose response
 - in the 25 mg/kg group, a 24% increase in blood urea nitrogen was noted on Day 58 after birth when compared with the control group. However, this was not considered toxicologically relevant as the value was the same as control on day 178 and there was no dose response compared to the 50 mg/kg group.
 - no treatment-related changes were noted in external parameter measurements in F1 animals between the control and test article groups

F₁ behavioral evaluation:

- no abnormalities were noted in pupil reflex, Preyer reflex, pain response or grip strength in any group
- no abnormalities were noted in gross ophthalmologic findings, slit-lamp findings, fundoscopic findings or electrocardiographic analysis in any group

F₁ functional evaluation:

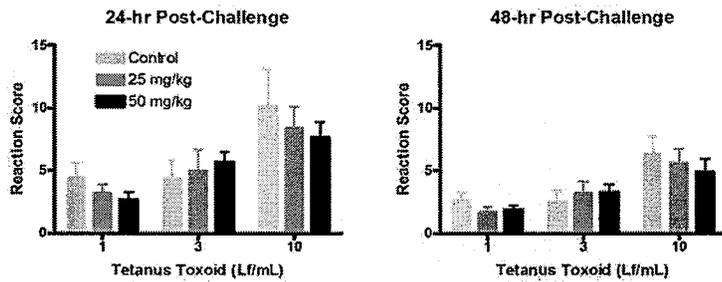
- immunology:
 - no significant differences were noted between the control and test article groups with respect to CD3+, CD3+/CD4+, CD3+/CD8+ and CD20+ lymphocyte counts or percentages in peripheral blood

Mean Lymphocyte Counts and Percentages in Peripheral Blood of F1 Cynomolgus Monkeys^a (Dams Treated from Day 50 of Gestation until Day 33 of Lactation with Golimumab)												
Dose (mg/kg)	CD3 ⁺			CD3 ⁺ /CD4 ⁺			CD3 ⁺ /CD8 ⁺			CD20 ⁺		
	BD 62	BD 92	BD 180	BD 62	BD 92	BD 180	BD 62	BD 92	BD 180	BD 62	BD 92	BD 180
COUNT (10 ³ /mm ³)												
0	8±5	6±2	8±3	6±4	4±1	5±2	2±2	2±1	3±1	6±5	3±2	3±2
25	8±8	6±2	7±2	6±5	4±1	4±2	2±2	2±1	2±1	5±6	3±2	2±1
50	11±10	4±2	6±2	7±6	3±2	4±1	3±3	1±1	2±1	10±9	3±2	3±1
PERCENTAGE												
0	60±8	67±8	69±8	41±7	46±7	45±10	18±4	21±4	23±6	37±7	28±8	27±8
25	61±8	65±9	70±8	43±6	44±8	46±6	18±3	21±4	23±3	34±8	31±6	26±7
50	53±11	59±9	63±12	36±8	40±6	39±10	16±4	19±3	22±5	41±10	36±9	31±8

a – n = 8-11/group, values rounded up at 0.5 or down

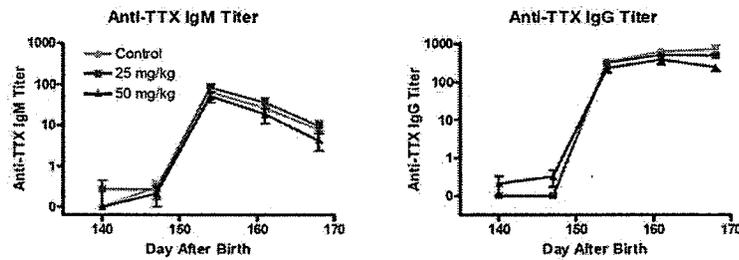
- no treatment-related change was observed in any group in delayed-type hypersensitivity reaction to tetanus toxoid (TTX), since no

significant differences were observed in the size of edema between the test article groups (see figure)

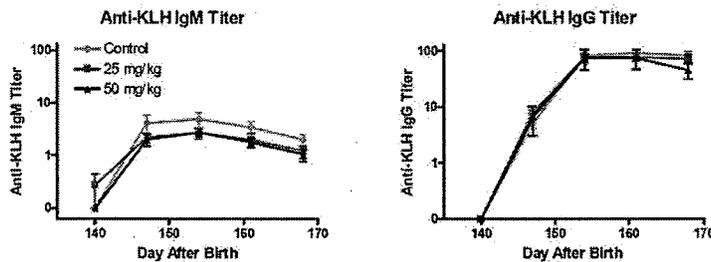


Effects of maternal golimumab treatment during pregnancy and lactation on the infant DTH response to intradermal administration of TTX

- no treatment-related change was observed in any group in antibody production of IgM and IgG to tetanus toxoid and KLH (see figures)



Effects of maternal golimumab treatment during pregnancy and lactation on the infant antibody response to TTX



Effects of maternal golimumab treatment on the infant antibody response to KLH immunization

- in six dam-F1 pairs, the dam was antibody positive while the F1 animal was negative (two pairs were in the saline control group and the remaining four pairs were in the low dose group)
- two dam-F1 pairs from the control group contained both dams and F1

- animals that were weakly antibody positive
- investigated by sponsor but no explanation found

F₁ gross pathology:

- a small thymus was noted in the gross pathological findings of one of two dead fetuses/neonates
- the dams of these F₁s had premature delivery with one having erosion/ulceration and induration in the papillary area
- no abnormal change was noted in any other F₁ animal on Day 180 after birth or at the additional necropsy

F₁ histology:

- nothing remarkable for either necropsy (day 180 or days 209-235 after birth), including immunohistochemical staining of bone marrow, thymus, spleen, Peyer's patches and lymph nodes

F₁ reproduction: not conducted

F₂ findings: no F₂ part of this study

Toxicokinetics: see table for F₀ animals for values

- neonatal levels of drug were near zero by six months after birth (day 180 - maternal dosing stopped on day 33 after birth)

2.6.6.9 Discussion and Conclusions -

2.6.6.10 Tables and Figures

2.6.7 TOXICOLOGY TABULATED SUMMARY – applicant's tables for repeat dose, reproductive toxicology, and local tolerance studies in monkeys (golimumab) and repeat dose and developmental toxicology studies in mice (anti-mouse TNF α mAb cV1q).

**Appears This Way
On Original**

**Repeat Dose Toxicity and Developmental Toxicity Studies (IV and SC)
in Monkeys with Golimumab**

1-Month IV Monkey

Test Article: Golimumab

Report Title: 1-Month Intravenous Dose Toxicity Study in Cynomolgus Monkeys with Golimumab							Study No.: T-2000-007
Species/Strain: Cynomolgus Monkey/ Macaca fascicularis		Duration of Dosing: 1 month		Location in CTD: 4.2.3.2			
Age at First Dose: Young Adult (2 – 4 kg)		Duration of Postdose: 37 days		Route: Intravenous			
Date of First Dose: November 3, 2000		Vehicle/Formulation: 20 mg/mL in 0.01 M sodium phosphate, 10% sucrose, pH 6		GLP Compliance: GLP			
Special Features: Safety Pharmacology/ Immunotoxicity							
No Observed Adverse Effect Level: 50 mg/kg							
Weekly Dose (mg/kg)	0 (Control)		10		50		
No. of Animals	M:5	F:5	M:5	F:5	M:5	F:5	
Toxicokinetics:							
No. of Animals	M:5	F:5	M:5	F:5	M:5	F:5	
First Dose (Day 1)							
C_{max} (µg/mL)	0	0	1253.08	377.57	2446.32	2731.02	
C_{min} (µg/mL)	-	-	-	-	-	-	
Noteworthy Findings							
Died or Sacrificed Moribund	0	0	0	0	0	0	
Body Weight - Day 1 (kg)	2.80	2.84	-	-	-	-	
Body Weight - Day 22 (kg)	2.96	2.94	-	-	-	-	
Food Consumption	-	-	-	-	-	-	
Clinical Observations	-	-	-	-	-	-	
Ophthalmoscopy	-	-	-	-	-	-	
Physical Examination	-	-	-	-	-	-	
Electrocardiography							
QRS - Day 10	38	-	1.18*	-	-	-	
QRS - Day 29	38	-	1.18*	-	-	-	
Heart Rate (bpm)	-	-	-	-	-	-	
Body temperature (°C)	100.88	99.84	-	-	-	-	

For controls, group means are shown. For treated groups, multiples of controls are shown. Statistical significance is based on actual data (not on the multiples of control). A noteworthy finding is defined as a significant difference of greater than 10% versus control that was not present prior to treatment.

*p < 0.05

- No noteworthy findings

Test Article: Golimumab

Report Title: One-Month Intravenous Dose Toxicity Study in Cynomolgus Monkeys with Golimumab							Study No.: T-2000-007
Weekly Dose (mg/kg)	0 (Control)		10		50		
No. of Animals	M:5	F:5	M:5	F:5	M:5	F:5	
Hematology							
Monocytes (10³/µL) - Day 9	-	0.358	-	-	-	0.08*	
Monocytes (%) - Day 9	-	1.4	-	-	-	0.14*	
Coagulation							
Serum Chemistry							
Total Bilirubin (mg/dL) - Pre-Tx	0.12	-	1.83*	-	-	-	
AST (U/L) - Day 29	41.2	-	1.62*	-	1.77*	-	
Organ Weights							
Gross Pathology							
Histopathology							
Additional Examinations							
Immunopathology (CD3, CD20)							
Lymphocyte Subset Analysis							
CD20 (%) - Day 29	-	10.488	-	2.15*	-	-	
Cytokines							
Anti-KLH							

For controls, group means are shown. For treated groups, multiples of control values are shown. Statistical significance is based on actual data (not on the multiples of control). A noteworthy finding is defined as a significant difference of greater than 10% versus control that was not present prior to treatment.

* p < 0.05

- No noteworthy findings

25-Week IV Monkey

Test Article: Golimumab

Report Title: 25-Week Intravenous Dose Toxicology Study with Golimumab in Cynomolgus Monkeys with a 12-Week Recovery Period						
Species/Strain: Cynomolgus Macaque			Duration of Dosing: 25-Weeks		Study No.: T-2004-006	
Age at First Dose: Young Adult (2-4 kg)			Duration of Postdose: 12-Weeks		Location in CTD: 4.2.3.2	
Date of First Dose: July 28, 2004			Route: Intravenous			
Vehicle/Formulation: 0.9% Sodium Chloride for Injection, USP/100 mg/mL in 0.01 M sodium phosphate, 8.5% sucrose and 0.01% polysorbate 80, pH 6						GLP Compliance: GLP
Special Features: Safety Pharmacology, Immunotoxicity						
No Observed Adverse Effect Level: 50 mg/kg						
Weekly Dose (mg/kg)	0 (Control)		25		50	
No. of Animals	M:8	F:8	M:8	F:8	M:8	F:8
Toxicokinetics:						
No. of Animals	M:8	F:8	M:8	F:8	M:8	F:8
AUC₀₋₂₄ or day 1-7 (µg·day/mL)						
First Dose - Day 1	0	0	1173	1921	4849	4499
Last Dose - Day 169	0	0	5247	6513	11115	12155
Cmax (µg/mL)						
First Dose - Day 1	0	0	771	829	1870	1805
Last Dose - Day 169	0	0	1655	1577	2819	2437
Noteworthy Findings						
Died or Sacrificed Moribund	0	0	0	0	0	0
Body Weight (Day -1)	2.44	2.36	-	-	-	-
Body Weight (Day 91)	2.78	2.68	-	-	-	-
Food Consumption	-	-	-	-	-	-
Clinical Observations						
Soft Feces	2/8	3/8	4/8	6/8	3/8	4/8
Physical Examinations						
Ophthalmic Examinations	-	-	-	-	-	-
Cardiovascular Parameters						
Mean Pressure (mmHg) - Week 13	87.9	-	0.84*	-	-	-
Systolic Pressure (mmHg) - Week 25	-	127	-	0.89*	-	0.88*

For controls, group means are shown. For treated groups, multiples of control/baseline are shown. Statistical significance is based on actual data (not on the multiples of control/baseline). Definition of noteworthy findings for clinical pathology is a significant difference of greater than 10% when compared to vehicle control that was not present prior to treatment. - No noteworthy findings. * p<0.05

Test Article: Golimumab

Report Title: 25-Week Intravenous Dose Toxicology Study with Golimumab in Cynomolgus Monkeys with a 12-Week Recovery Period					Study No.: T-2004-006	
Period						
Weekly Dose (mg/kg)	0 (Control)		25		50	
No. of Animals	M:8	F:8	M:8	F:8	M:8	F:8
Hematology						
Monocytes - Day 29 (%)	-	3.4	-	0.74*	-	0.71*
Monocytes - Day 176 (%)	-	3.2	-	0.50*	-	-
WBC - Day 176 (10³/µL)	-	9.98	-	-	-	1.62*
Serum Chemistry*						
Triglyceride - Day 176 (mg/dL)	-	35.4	-	-	-	1.62*
Organ Weights						
Thymus/Bwt - Day 176	0.06	-	3.33*	-	-	-
Gross Pathology - Day 253						
Number Examined	2	2	2	2	2	2
Lungs w/bronchi: Discoloration	0	0	1	0	0	0
Spleen: Enlarged	0	0	1	0	0	0
Histopathology - Day 253						
Number Examined	2	2	2	2	2	2
Heart: Histiocytic infiltration - Grade 2	0	0	1	0	0	0
Liver: Granulomatous inflammation - Grade 3	0	0	1	0	0	0
Lungs: Alveolar hemorrhage - Grade 3	0	0	1	0	0	0
Lungs: Pigmented macrophages - Grade 2	0	0	1	0	0	0
Kidneys: Glomerulopathy - Grade 1	0	0	1	0	0	0
Kidneys: MCI, interstitial - Grade 2	0	0	1	0	0	0

For controls, group means are shown. For treated groups, multiples of control/baseline values are shown. Statistical significance is based on actual data (not on the multiples of control/baseline). Definition of noteworthy findings for clinical pathology is a significant difference of greater than 10% when compared to vehicle control that was not present prior to treatment.

* p<0.05

- No noteworthy findings

Report Title: 25-Week Intravenous Dose Toxicology Study with Golimumab in Cynomolgus Monkeys with a 12-Week Recovery Period						Test Article: Golimumab	
Study No.: T-2004-006							
Weekly Dose (mg/kg)	0 (Control)		25		50		
No. of Animals	M:8	F:8	M:8	F:8	M:8	F:8	
Additional Examinations							
Immunotoxicity							
Immunohistopathology (CD3, CD20)							
Immunophenotyping Lymphocyte Subsets							
CD20+ - Day 2 (% baseline)	0.87	0.65	1.54*	-	1.54*	1.54*	
CD20+ - Day 29 (% baseline)	0.96	-	1.50*	-	1.32*	-	
CD20+ - Day 92 (% baseline)	0.93	0.73	1.67*	1.62*	1.91*	2.14*	
CD20+ - Day 176 (% baseline)	0.74	0.63	1.88*	-	2.82*	2.25*	
CD3+ - Day 2 (% baseline)	0.80	-	1.44*	-	1.63*	-	
CD3+ - Day 92 (% baseline)	1.08	0.94	-	-	1.70*	1.49*	
CD3+ - Day 176 (% baseline)	0.89	-	1.73*	-	2.16*	-	
CD3+/CD4+ - Day 2 (% baseline)	0.85	-	1.40*	-	1.61*	-	
CD3+/CD4+ - Day 92 (% baseline)	-	0.98	-	-	-	1.40*	
CD3+/CD4+ - Day 176 (% baseline)	0.97	-	-	-	1.81*	-	
CD3+/CD44+ - Day 2 (% baseline)	2.05	1.55	-	1.81*	1.47*	-	
CD3+/CD45RA+ - Day 2 (% baseline)	0.80	-	-	-	1.75*	-	
CD3+/CD45RA+ - Day 92 (% baseline)	1.30	1.04	-	-	1.61*	1.81*	
CD3+/CD45RA+ - Day 176 (% baseline)	0.99	-	1.69*	-	2.26*	-	
CD3+/CD8+ - Day 2 (% baseline)	0.78	-	1.42*	-	1.72*	-	
CD3+/CD8+ - Day 92 (% baseline)	0.99	0.92	1.82*	-	2.08*	1.62*	
CD3+/CD8+ - Day 176 (% baseline)	0.87	-	2.07*	-	2.53*	-	
CD3-/CD14+ - Day 29 (% baseline)	-	1.19	-	0.60*	-	0.65*	
Lymphocytes - Day 2 (% baseline)	0.86	-	1.38*	-	1.53*	-	
Lymphocytes - Day 29 (% baseline)	0.99	-	1.34*	-	1.25*	-	
Lymphocytes - Day 92 (% baseline)	1.05	0.89	1.55*	1.35*	1.59*	1.64*	
Lymphocytes - Day 176 (% baseline)	0.88	-	1.75*	-	1.94*	-	
Monocytes - Day 29 (% baseline)	-	1.03	-	0.82*	-	-	

For controls, group means are shown. For treated groups, multiples of control/baseline are shown. Statistical significance is based on actual data (not on the multiples of control/baseline). Definition of noteworthy findings for clinical pathology is a significant difference of greater than 10% when compared to vehicle control that was not present prior to treatment.
 - No noteworthy findings: * p<0.05

Appears This Way
On Original

6-Month SC Monkey

Test Article: Golimumab

Report Title: 6-Month Subcutaneous Dose Toxicity Study with Golimumab in Cynomolgus Monkeys with a 12-Week Recovery Period						
Species/Strain: Cynomolgus Monkey	Duration of Dosing: 6-months		Study No.: T-2002-001			
Weight at First Dose: Young Adult (2 – 4 kg)	Duration of Postdose: 12-weeks		Location in CTD: 4.2.3.2			
Date of First Dose: Week of July 7, 2002	Route: Subcutaneous					
Control/Formulation: 0.9% sodium Chloride/100 mg/mL in 0.01 M sodium phosphate, 8.5 % sucrose, 0.01% polysorbate 80, pH 6						GLP Compliance: GLP
Special Features: Immunotoxicity						
No Observed Adverse Effect Level: 50 mg/kg						
Twice Weekly Dose (mg/kg)	0 (Control)		25		50	
No. of Animals	M:8	F:8	M:8	F:8	M:8	F:8
Toxicokinetics:						
No. of Animals	M:8	F:8	M:8	F:8	M:8	F:8
AUC (µg·day/mL) *						
Day 1 - 4	-	-	419	534	770	742
Day 179 - 182	-	-	2399	2845	4488	6826
Cmax (µg/mL)						
First Dose – Day 1	-	-	191	204	395	469
Last Dose – Day 179	-	-	1193	1045	2491	2427
Noteworthy Findings						
Died or Sacrificed Moribund	0	0	0	0	0	0
Body Weight (Day 1)	2.58	2.51	-	-	-	-
Body Weight (Day 85)	2.86	2.76	-	-	-	-
Food Consumption	-	-	-	-	Slightly Low	-
Clinical Observations						
Administration Site Edema	-	-	+(1)	+(3)	+(1)	+(2)
Physical Examinations	-	-	-	-	-	-
Ophthalmoscopy	-	-	-	-	-	-
Electrocardiography	-	-	-	-	-	-
Cardiovascular Parameters						
Systolic Blood Pressure (mm Hg) – Week 5	109.8	-	0.59*	-	-	-
Mean Blood Pressure (mm Hg) – Week 5	78.8	-	0.68*	-	-	-

* Calculated for two animals per sex per group. For controls, group means are shown. For treated groups, multiples of control values are shown. Statistical significance is based on actual data (not on the multiples of control). The definition of noteworthy is a significant difference versus control that was not present at baseline: * - p<0.05; - No noteworthy findings

Appears This Way
On Original

Test Article: Golimumab

Report Title: 6-Month Subcutaneous Dose Toxicity Study with Golimumab in Cynomolgus Monkeys with a 12-Week Recovery Period					Study No.: T-2002-001	
Twice Weekly Dose (mg/kg)	0 (Control)		25		50	
No. of Animals	M:8	F:8	M:8	F:8	M:8	F:8
Hematology						
Lymphocytes (%) – Day 22	42.8	-	0.65*	-	-	-
Neutrophils (10 ³ /µL) – Day 22	5.133	-	1.87*	-	-	-
WBC (10 ³ /µL) – Day 22	10.31	-	1.39*	-	-	-
Monocytes (10 ³ /µL) – Day 22	0.288	-	1.40*	-	-	-
Monocytes (%) – Day 22	3.0	-	-	-	0.77*	-
Monocytes (%) – Day 22	4.4	-	-	-	0.73*	-
Eosinophils (%) – Day 183	-	3.0	-	-	-	0.40*
Coagulation						
Serum Chemistry						
K (meq/L) – Day 92	-	4.18	-	-	-	1.20*
Globulin (g/dL) – Day 92	3.23	-	-	-	1.12*	-
A/G Ratio – Day 92	1.40	-	-	-	0.85	-
Cholesterol (mg/dL) – Day 183	-	107.2	-	-	-	0.84*
ALT (U/L) – Day 183	54.2	-	-	-	0.72*	-
Urinalysis						
Organ Weights						
Gross Pathology						
Histopathology*						
Number Examined – Day 92	3	3	3	3	3	3
Subcutaneous inflammation – Day 92	-	1 (1)	2 (1-2)	3 (1-3)	3 (1-3)	2 (1-2)
Number Examined – Day 183	3	3	3	3	3	3
Subcutaneous inflammation – Day 183	2 (1)	2 (1)	3 (2-3)	2 (2-3)	3 (1-2)	2 (2)
Number Examined – Day 267 (Recovery)	2	2	2	2	2	2
Subcutaneous inflammation – Day 267*	-	-	1 (1)	1 (1)	-	1 (1)

*Number of animals affected (range of severity on a scale of 1-4)

For controls, group means are shown. For treated groups, multiples of control values are shown. Statistical significance is based on actual data (not on the multiples of control). The definition of noteworthy is a significant difference versus control that was not present at baseline. * - p<0.05; - No noteworthy findings

Test Article: Golimumab

Report Title: 6-Month Subcutaneous Dose Toxicity Study with Golimumab in Cynomolgus Monkeys with a 12-Week Recovery Period					Study No.: T-2002-001	
Twice Weekly Dose (mg/kg)	0 (Control)		25		50	
No. of Animals	M:8	F:8	M:8	F:8	M:8	F:8
Additional Examinations						
Immunohistopathology						
Immunophenotyping Lymphocyte Subsets						
Absolute Lymphocytes (10 ³ /µL) – Day 2	4.921	-	-	-	1.49*	-
CD3+ T-Lymphocytes (10 ³ /µL) – Day 2	-	2.756	-	-	1.52*	-
CD3+ T-Lymphocytes (10 ³ /µL) – Day 86	-	3.800	-	1.47*	-	-
CD3+CD44+ (10 ³ /µL) – Day 86	-	2.043	-	1.53*	-	-
CD3+CD45RA+ (10 ³ /µL) – Day 86	-	3.203	-	1.52*	-	1.28*
CD4+ T-Lymphocytes (10 ³ /µL) – Day 86	-	1.976	-	1.49*	-	-
CD8+ T-Lymphocytes (10 ³ /µL) – Day 2	1.021	-	-	-	1.67*	-
CD8+ T-Lymphocytes (10 ³ /µL) – Day 86	-	1.816	-	1.45*	-	-
CD20+ B-Lymphocytes (10 ³ /µL) – Day 2	0.693	-	-	-	1.82*	-
CD20+ B-Lymphocytes (10 ³ /µL) – Day 86	0.756	-	-	-	2.06*	-
Antibody Response to KLH						
	-	-	-	-	-	-

For controls, group means are shown. For treated groups, multiples of control value is shown. Statistical significance is based on actual data (not on the multiples of control). The definition of noteworthy is a significant difference versus control that was not present at baseline.

* p<0.05

- No noteworthy findings

Embryo-Fetal Development SC Monkey

Test Article: Golimumab

Effects on Embryo-Fetal Development			
Report Title: A Study for the Effect of Golimumab on Embryofetal Development in Cynomolgus Monkeys by Twice Weekly Subcutaneous Administration			
Design Similar to ICH 4.1.3?	Yes	Duration of Dosing: GD 20 – GD 51	Study No.: T-2003-005
Species/Strain: Cynomolgus Macaque		Day of Mating: Day 0	Location in CTD: 4.2.3.5.2
Age at First Dose: 4.3 – 8.2 years		Day of C-Section: GD 100 - 103	GLP Compliance: Yes
Date of First Dose: May 5, 2003		Route: Subcutaneous	
Special Features: Immunotoxicity		Vehicle/Formulation: 0.9 % Saline USP/ 100 mg/mL in 0.01M Sodium Phosphate, 8.3% Sucrose, 0.01% polysorbate 80, pH6	
No Observed Adverse-Effect Level:			
F ₀ Females: 50 mg/kg, F ₁ Litters: 50 mg/kg			
Twice Weekly Dose (mg/kg)	0 (Control)	25	50
Dams: Toxicokinetics			
AUC ₀₋₅₁ (µg·day/mL)	-	10025.11	27051.53
C _{max} (µg/mL)	-	655.53	1613.14
No. Pregnant	12	12	14
No. Died or Sacrificed Moribund	0	0	0
No. Aborted or No. Fetal Deaths	2	0	0
Noteworthy Findings			
Hematology (Dams)			
Monocytes (%)	3.86	0.70*	-
Lymphocytes (10 ³ /µL) – GD35	4.908	1.50*	-
Lymphocytes (10 ³ /µL) – GD52	4.695	1.58*	-
Basophils (10 ³ /µL) – GD52	0.025	2.16*	-
Lymphocyte Subset Analysis			
CD3+ T-lymphocytes (10 ³ /µL) – GD35	3.38	1.54*	-
CD3+ T-lymphocytes (10 ³ /µL) – GD52	3.27	1.65*	-
CD4+ T-lymphocytes (10 ³ /µL) – GD35	1.79	1.63*	-
CD4+ T-lymphocytes (10 ³ /µL) – GD52	1.72	1.75*	-
CD45+ Lymphocytes (10 ³ /µL) – GD35	4.55	1.55*	-
CD45+ Lymphocytes (10 ³ /µL) – GD52	4.54	1.56*	-
CD20+ Lymphocytes (10 ³ /µL) – GD35	0.95	1.65*	-

For controls, group means are shown. For treated groups, multiples of controls are shown. Statistical significance is based on actual data (not on the multiples of control). The definition of noteworthy is a significant difference versus control that was not present at baseline. * p<0.05, - No noteworthy findings, GD = Gestation Day

Test Article: Golimumab

Effects on Embryo-Fetal Development			
Report Title: A Study for the Effect of Golimumab on Embryofetal Development in Cynomolgus Monkeys by Twice Weekly Subcutaneous Administration			Study No.: T-2003-005
Twice Weekly Dose (mg/kg)	0 (Control)	25	50
Litters: No. of Litters Evaluated	10	12	10
No. Live Fetuses	10	12	10
No. of Abortions	1	0	0
No. Dead Fetuses	1	0	0
Mean Fetal Body Weight (g)	113	114.4	115.9
Fetal Sex Ratios (% males)	36.4	33.3	10
Fetal Anomalies:	-	-	-
Skeletal Anomalies:	-	-	-

For controls, group means are shown. For treated groups, multiples of controls are shown. Statistical significance is based on actual data (not on the multiples of control). The definition of noteworthy is a significant difference versus control that was not present at baseline. * p<0.05, - No noteworthy findings, GD = Gestation Day

Peri- and Post-Natal SC Monkey

Test Article: Golinumab, Lot D03PA7222 and D03PG7263

Effects on Pre- and Postnatal Development, Including Maternal Function			
Report Title: A Study for the Effect of Golinumab on Pre- and Postnatal Development, including Maternal Function in Cynomolgus Monkeys by Twice Weekly Subcutaneous Administration			
Design Similar to ICH 4.1.1? Yes	Duration of Dosing: F: Day 50 of gestation to Day 33 after delivery	Study No.: T-2004-007	
Species/Strain: <i>Macaca fascicularis</i>	M: 0 (used for mating only)	Location in CTD: 4.2.3.5.3	
Age at First Dose: 3 to 10 years old	Day of first mating: F: 27-Jul 2004	GLP Compliance: Yes.	
Date of First Dose: 16-Sep 2004	Day of C-Section: Not applicable		
Special Features: Immunotoxicity in Neonates	Route: Subcutaneous		
No Observed Adverse Effect Level: F ₀ : 50 mg/kg F ₁ : 50 mg/kg	Vehicle/Formulation: Each 1 mL of the golinumab formulation contained 100 mg golinumab, 85 mg sucrose, 1.27 mg monobasic sodium phosphate monohydrate, 0.14 mg dibasic sodium phosphate dihydrate and 0.1 mg polysorbate 80, pH 5.5-6.5. The reconstituted solution was light yellow and free of foreign particles.		
Dosing Phase: 18 to 22 weeks Recovery Phase: 21 weeks			
F ₀			
Twice weekly Dose (mg/kg)	0 (Control 0.9% sodium chloride for injection)	25	50
No. of Animals	12	12	12
Toxicokinetics:			
No. of Animals	12	12	12
C _{max} (µg/mL)			
First dose (after Day 50 of gestation)		176.32 ± 100.11	321.04 ± 255.52
Last dose (after Day 33 after delivery)		851.04 ± 355.16	1481.87 ± 813.04

Test Article: Golinumab

Effects on Pre- and Postnatal Development, Including Maternal Function			
Report Title: A Study for the Effect of Golinumab on Pre- and Postnatal Development, including Maternal Functioning in Cynomolgus Monkeys by Twice Weekly Subcutaneous Administration			Study No.: T-2004-007
F ₀			
Twice weekly Dose (mg/kg)	0 (Control 0.9% sodium chloride for injection)	25	50
No. of Animals	12	12	12
Day 60 after delivery	-	214.13 ± 79.37	387.47 ± 259.17
t _{1/2} (after delivery)	-	16.61 ± 6.43	29.47 ± 21.54
Noteworthy Findings			
No. Pregnant	12	12	12
No. Died or Sacrificed Moribund	0	0	0
No. Aborted	1 (GD117)	0	0
No. Stillbirth	2 (GD160, GD130)	0	3 (GD159, GD150, GD163)
Clinical Observations			
Body Weight	-	-	-
Food consumption	-	-	-
Hematology	-	-	-
Serum Biochemistry			
Potassium ^a	5.01	-	1.09*
Duration of Gestation (days)	154 to 165	140 to 167	149 to 172
No. with Abnormal Parturition	-	-	-
Necropsy Observations			
Papillary Area	-	-	-
Erosion / Ulcer	-	-	1
Induration	-	-	1

GD = Gestation Day
^a GD49. For treated groups, noteworthy findings are expressed as multiples of control values.
 - No noteworthy findings; * p<0.05

Test Article: Golimumab

Effects on Pre- and Postnatal Development, Including Maternal Function			
Report Title: A Study for the Effect of Golimumab on Pre- and Postnatal Development, including Maternal Functioning in Cynomolgus Monkeys by Twice Weekly Subcutaneous Administration		Study No.: T-2004-007	
F₁			
Twice weekly Dose (mg/kg)	0 (Control 0.9% sodium chloride for injection)	25	50
Toxicokinetics:			
No. of Animals	9	10	8
Day 30 after birth (µg/mL)		140.07 ± 48.59	274.09 ± 124.16
t _{1/2} (after delivery)		22.96 ± 1.59	22.82 ± 2.84
No. Evaluated	9	12	9
No. Died	0	1 (B1)	1 (B11)
Clinical Observations			
Animals that Survived	-	-	-
Animals that Died	-	-	-
Emaciation	-	-	1
Prone Position	-	-	1
Body Weight	-	-	-
Hematology			
Neutrophilic Leukocyte ^b	18.74	-	1.48**
Lymphocyte ^c	75.81	-	0.87**
Serum Biochemistry			
Total Cholesterol ^f	124.6	1.21*	-
Blood Urea Nitrogen ^e	10.47	1.24*	-
Immunological Findings	-	-	-
Functional Development	-	-	-
Morphological Development	-	-	-
Immunological Development	-	-	-
Necropsy Observations (Day 180 after birth):			
No. Evaluated	6	6	6
Gross Pathological Findings	-	-	-

B= Day after birth
^b Day 178 after birth. ^c Day 58 after birth. For treated groups, noteworthy findings are expressed as multiples of control values.
 - No noteworthy findings: * - p<0.05, ** - p<0.01

Test Article: Golimumab

Effects on Pre- and Postnatal Development, Including Maternal Function			
Report Title: A Study for the Effect of Golimumab on Pre- and Postnatal Development, including Maternal Functioning in Cynomolgus Monkeys by Twice Weekly Subcutaneous Administration		Study No.: T-2004-007	
F₁			
Twice weekly Dose (mg/kg)	0 (Control 0.9% sodium chloride for injection)	25	50
No. of Animals	9	10	8
Histopathological Findings			
H. and E. Staining			
Liver			
Extramedullary Hematopoiesis in Gilsson's Sheath	1	1	2
Microgranuloma	1	1	2
Immunohistochemical Staining ^b	-	-	-
Necropsy Observations (additional necropsy)^d:			
No. Evaluated	3	5	2
Gross Pathological Findings	-	-	-
Histopathological Findings			
H. and E. Staining			
Liver			
Extramedullary Hematopoiesis in Gilsson's Sheath	0	2	0
Spleen			
Decreased Lymphocytes in the White Pulp	0	1	0

GD = Gestation day; B = Day after birth
^a Day 49 of gestation.
^b Day 178 after birth.
^c Day 58 after birth.
^d Day 209 to Day 235 after birth.
 - No noteworthy findings: * - p<0.05, ** - p<0.01; For treated groups, noteworthy findings are expressed as multiples of control

Repeated Dose and Developmental Toxicology Studies in Mice (IV) with cV1q anti-mouse TNF α monoclonal antibody cV1q muG2a

6-Month IV Mouse

Test Article: cV1q

Report Title: 6-Month Chronic Toxicity Study in Mice with cV1q muG2a (cV1q) Anti-Mouse TNF α Monoclonal Antibody						
Species/Strain: Mouse/CD-1	Duration of Dosing: 3 or 6 months		Study No.: T-098-004			
Age at First Dose: 4 - 5 Weeks	Duration of Postdose: 3 months		Location in CTD: 4.2.3.2			
Date of First Dose: August 3, 1999	Route: Intravenous					
Vehicle/Formulation: 1x Dulbecco's phosphate buffered saline			GLP Compliance: Yes			
Special Features:						
No Observed Adverse Effect Level: 40 mg/kg						
Weekly Dose (mg/kg)	0 (Control)		10		40	
No. of Animals	M: 30	F: 30	M: 30	F: 30	M: 30	F: 30
Toxicokinetics:						
No. of Animals	M: 10 - 20	F: 10 - 20	M: 10 - 20	F: 10 - 20	M: 10 - 20	F: 10 - 20
Concentration (μ g/mL)						
Day 91 (6 days post dose)	-	-	410	304	1378	1459
Day 182 (8 days post dose)	-	-	309	201	693	620
Noteworthy Findings						
Died or Sacrificed Moribund	3	0	1	0	2	1
Body Weight - Day 176	43.48	33.69	-	-	-	-
Food Consumption - Day 176	6.1	6.2	-	-	-	-
Clinical Observations						
Ophthalmoscopy	-	-	-	-	-	-

-No noteworthy findings

Noteworthy findings are defined as a statistical difference of greater than 10% versus the control group

Test Article: cV1q

Report Title: 6-Month Chronic Toxicity Study in Mice with cV1q muG2a (cV1q) Anti-Mouse TNF α Monoclonal Antibody					Study No.: T-098-004	
Weekly Dose (mg/kg)	0 (Control)		10		40	
No. of Animals	M:30	F:30	M:30	F:30	M:30	F:30
Hematology ^a						
WBC ($10^3/\mu$ L) - Week 13	-	3.60	-	2.19*	-	-
Lymphocytes - Week 13	-	3.234	-	2.01*	-	-
Serum Chemistry ^a						
Total Bilirubin (mg/dL) - Week 13	0.28	-	-	-	1.5*	-
AST (U/L) - Week 26	169.4	92.2	1.60*	1.46*	-	-
Total Protein (g/dL) - Week 26	-	6.17	-	-	-	1.10*
Globulin (g/dL) - Week 26	-	2.10	-	-	-	1.14*
ALP (U/L) - Week 39	-	104.2	-	0.63*	-	-
Organ Weights ^a						
Adrenal Glands (g) - Week 13	0.00509	-	1.12*	-	-	-
Adrenal Glands/Bwt - Week 13	0.01423	-	1.49*	-	-	-
Adrenal/Brain Wt - Week 13	1.01296	-	1.44*	-	-	-
Pituitary Gland (g) - Week 13	0.00329	-	1.30*	-	1.19*	-
Pituitary Gland/Bwt - Week 13	0.00921	-	1.36*	-	1.23*	-
Pituitary Gland/Brain Wt - Week 13	0.66014	-	1.31*	-	1.17*	-
Gross Pathology						
Histopathology	-	-	-	-	-	-

^a For controls, group means are shown. For treated groups, multiples of control values are shown. Statistical significance is based on actual data (not on the multiples of control/baseline). The definition of noteworthy is a statistically significant difference versus control of greater than 10%.

- No noteworthy findings

* - p<0.05

Fertility and Early Embryonic Development IV Mouse

Test Article: cV1q muG2a (C258A)

Fertility and Early Embryonic Development to Implantation			
Report Title: Intravenous Dosage Fertility and General Reproduction Toxicity Study of cV1q muG2a (C258A) Anti-Mouse TNF Antibody in Mice			Study No.: T-098-003
Design Similar to ICH 4.1.1 Including Male Fertility Addendum? Yes	Duration of Dosing: Females: Once weekly beginning two weeks prior to mating and on GD 0 and GD 7 Males: Once weekly beginning 8 weeks prior to mating through cohabitation and the week before sacrifice (12 weeks total)		Location in CTD: 4.2.3.5.1
Species/Strain: CD-1®(ICR)BR mice	Day of Mating: GD 0		
Age at First Dose: Males: 69 days Females: 93 days	Date of First Dose: 23 JUL 1998 (males) 03 SEP 1998 (females)		GLP Compliance: Yes
Special Features:		Route: Intravenous	
No Observed Adverse Effect Level:		Vehicle/Formulation: 1X Dulbecco's Phosphate Buffered Saline	
F ₀ Males: > 40 mg/kg			
F ₀ Females: > 40 mg/kg			
F ₀ Conceptuses: > 40 mg/kg			
F ₀ Males			
Dose (mg/kg)	0 (Vehicle)	10	40
No. of Animals	25	25	25
Pharmacokinetics:			
No. of Animals	24	24	23
Mean Concentration of cV1q in maternal sera (µg/mL)			
Males (collected 7 days from last infusion)	No detectable levels	408.7	1021.0
Immune Response (Antigenicity):			
Percentage of positive response (Males)	12.5	87.5	62.5
Noteworthy Findings			
No. Died or Sacrificed Moribund	1	1	2
Clinical Observations	-	-	-
Body Weight (Terminal)	39.1 g	-	-
Body Weight Gain	3.2 g	-	-
Precoital Interval	2.2	2.8	3.2

* After twelve weekly doses. For controls, group means are shown. Precoital interval = mean number of days prior to mating.
GD = Gestational Day; - No noteworthy findings

Test Article: cV1q muG2a (C258A)

Fertility and Early Embryonic Development to Implantation			
Report Title: Intravenous Dosage Fertility and General Reproduction Toxicity Study of cV1q muG2a (C258A) Anti-Mouse TNF Antibody in Mice			Study No.: T-098-003
Weekly Dose (mg/kg)	0 (Vehicle)	10	40
No. of Animals	25	25	25
Noteworthy Findings (Continued)			
No. of Males that Mated/Copulation Rate ^a	24 / 100.0	24 / 100.0	21 / 91.3
No. of Fertile Males/Fertility Rate ^a	22 / 91.7	20 / 90.9	16 / 76.2
Necropsy Observations	-	-	-
Organ Weights	-	-	-
Sperm Motility, Count and Density	-	-	-
F ₀ Females			
No. of Animals	25	25	25
Pharmacokinetics:			
No. of Animals	25	21	22
Mean Concentration of cV1q in maternal sera (µg/mL)			
Females (collected 4 days from last infusion)	No detectable levels	85.44	370.9
Immune Response (Antigenicity):			
Percentage of positive response (Females)	12.5	52.0	19.0
Relevant Findings			
No. Died or Sacrificed Moribund	0	4	3
No. Aborted or with Total Resorption of Litter	0	0	0
Clinical Observations	-	-	-
Premating Body Weight ^b	27.7 g	-	-
Premating Body Weight Change	-0.2 g	0.4 g	0.5 g
Gestation Body Weight ^c	39.0 g	-	-
Gestation Body Weight Change ^c	10.5 g	-	-
Mean No. Estrous Cycles/14 days	2.9	2.9	2.7
Mean No. Days Prior to Mating	2.2	2.6	3.2
No. Females Mated	25	25	25
No. of Pregnant Females	23	21	19

^a Copulation rate = (no. of males that copulated/total no. of males on study) × 100; Fertility Rate = (no. of males that sired offspring/total no. of males that copulated) × 100.

^b After two weekly doses.

^c After four weekly doses.

Test Article: cV1q muG2a (C-0000)

Fertility and Early Embryonic Development to Implantation			
Report Title: Intravenous Dosage Fertility and General Reproduction Toxicity Study of cV1q muG2a (C-0000) Anti-Mouse TNF Antibody in Mice			Study No.: T-098-003
Weekly Dose (mg/kg)	0 (Vehicle)	10	40
No. of Animals	25	25	25
Relevant Findings (Continued)			
Necropsy Observations	-	-	-
Mean No. Corpora Lutea	13.6	14.1	14.1
Mean No. Implantations	12.3	12.8	12.9
Mean % Preimplantation Loss	8.6	9.3	8.6
Mean No. Live Conceptuses	11.7	12.2	12.7
Mean No. Dead Conceptuses	0.6	0.6	0.2
Mean % Postimplantation Loss	5.0	4.8	1.4

- No noteworthy findings

b(4)

Embryo-Fetal Development IV Mouse

Test Article: cV1q muG2a

Effects on Embryo-Fetal Development			
Report Title: Intravenous Development Toxicity Study of cV1q muG2a (C-0000) Anti-Mouse TNF Antibody in Mice			
Design Similar to ICH 4.1.3?	Yes	Duration of Dosing: GD 6 and 12	Study No.: T-096-011
Species/Strain: CD-1® (ICR)BR mice		Day of Mating: GD 0	Location in CTD: 4.2.3.5.2
Age at First Dose: ~ 75 days		Day of C-Section: GD 18	GLP Compliance: Yes
Date of First Dose: 19 MAR 1997		Route: Intravenous	
Special Features:		Vehicle/Formulation: 1X Dulbecco's Phosphate Buffered Saline	
No Observed Adverse-Effect Level:			
F ₀ Females: > 40 mg/kg			
F ₁ Litters: > 40 mg/kg			
Dose (mg/kg)	0 (Control)	10	40
No. of Animals	25	21	21
Pharmacokinetics:			
No. of Animals	8	8	8
Mean Concentration of cV1q in maternal sera (µg/mL)			
Day GD 14 (single dose)	< 0.39	4.1	27.6
Day GD 14 (two doses)	< 0.39	37.5	159.5
Day GD 18 (two doses)	< 0.39	0.8	7.2
Relevant Findings			
No. Pregnant	22	18	17
No. Died or Sacrificed Moribund	1	0	0
No. Aborted or with Total Resorption of Litter	0	1	0
Clinical Observations	-	-	-
Body Weight (G 18)	61.5 g	-	-
Body Weight Gain (G 6 to 18)	28.5 g	-	-
Mean No. Corpora Lutea	14.4	14.9	15.4
Mean No. Implantations	13.4	13.9	14.0
Mean % Preimplantation Loss	6.4	6.4	7.3
Necropsy Observations	-	-	-

*After two doses. GD = Gestation Day
- No noteworthy findings

b(4)

Test Article: cV1q muG2a

Effects on Embryo-Fetal Development			
Report Title:	Intravenous Development Toxicity Study of cV1q muG2a (C258A) Anti-Mouse TNF Antibody in Mice		Study No.: T-096-011
Dose (mg/kg)	0 (Control)	10	40
No. of Animals	25	21	21
Litters:	No. of Litters Evaluated	21	17
	No. Live Fetuses	265	229
	Mean No. Live Fetuses	12.6	13.5
	Mean No. Early Resorptions	0.7	0.2
	Mean No. Late Resorptions	0.1	0.2
	Mean No. Total Resorptions	0.8	0.5
	No. Dead Fetuses	1	1
	Mean No. of Dead Fetuses	0.0	0.0
	Mean % Postimplantation Loss	6.0	4.1
	Mean Fetal Body Weight (g)	1.39	1.33
	Fetal Sex Ratios (% males)	53.8	54.7
Fetal Anomalies:			
	Gross External	-	-
	Visceral Anomalies	-	-
	Skeletal Anomalies	-	-
	Total Affected Fetuses (Litters)	49 (19)	37 (16)
	No. Fetuses (%) ^a	18.0	16.4

^a Mean % fetuses with any alteration per litter.
 - No noteworthy findings

b(4)

Peri- and Post-Natal IV Mouse

Test Article: cV1q muG2a (C258A) Anti-Mouse TNF Antibody

Effects on Pre- and Postnatal Development, Including Maternal Function			
Report Title: Intravenous Developmental and Perinatal/Postnatal Reproduction Toxicity Study of cV1q muG2a (C258A) Anti-Mouse TNF Antibody in Mice, Including Postnatal Behavioral/Functional and Immunological Evaluations			
Design Similar to ICH 4.1.2?	Yes	Duration of Dosing: GD 6, 12 and 18 and LD 3, 9 and 15	Study No.: T-2001-002
Species/Strain:	CD-1® (ICR) BR mouse	Day of Mating: Day 0	Location in CTD: 4.2.3.5.3
Age at First Dose: 80 days		Route: Intravenous	GLP Compliance: Yes
Date of First Dose: 29 AUG 01	Vehicle/Formulation: 1 x Dulbecco's Phosphate Buffered Saline (DPBS) without Ca ⁺⁺ and Mg ⁺⁺ with 0.01% Tween® 80, pH 7.4		
Special Features: Immunotoxicity			
No Observed Effect Level:			
F ₀ Females: > 40mg/kg/dose			
F ₁ Males: > 40 mg/kg/dose			
F ₁ Females: > 40 mg/kg/dose			
F ₀ Females:			
Dose (mg/kg)	0	10	40
No. of Animals	25	25	25
No. Pregnant	23	23	23
No. Died or Sacrificed Moribund	1 ^a	4 ^a	3 ^a
No. Aborted or with Total Resorption of Litter	0	0	0
Clinical Observations ^b			
Soft or liquid feces	0 / 0	9 / 4 ^c	3 / 2 ^c
Gestation Body Weight (GD 18)	55.6 g	-	-
Gestation Body Weight Gain (GD 0 to 18)	30.6 g	-	-
Lactation Body Weight (LD 21)	44.3 g	-	-
Lactation Body Weight Gain (LD 1 to 21)	10.4 g	-	-
Mean Duration of Gestation (days)	19.9	-	-
No. with Abnormal Parturition	0	0	0
Necropsy Observations			
Mean Concentration of cV1q in sera (µg/mL)	< 0.2	43.4	240.5

^a Occurred during the lactation period.

^b N/N = Total number of observations / number of mice with observation.

^c After three days of dosing. For controls, group means are shown. After six days of dosing, for controls, group means are shown. For treated groups, noteworthy findings are expressed as multiples of control values. Statistical significance is based on actual data (not on the multiples of control).

GD = Gestation Day, LD = Lactation day; - No noteworthy findings.

b(4)

Test Article: cV1q muG2a (b(4)) Anti-Mouse TNF Antibody

Effects on Pre- and Postnatal Development, Including Maternal Function				
Report Title: Intravenous Developmental and Perinatal/Postnatal Reproduction Toxicity Study of cV1q muG2a (b(4)) Anti-Mouse TNF Antibody in Mice, Including Postnatal Behavioral/Functional and Immunological Evaluations			Study No.: T-2001-002	
Dose (mg/kg)		0	10	40
F₁ Litters:	No. of Litters Evaluated	23	23	23
(Prewearing)	Mean No. of Implantations / Delivered Litter	12.7	12.6	13.0
	Mean No. Pups/Litter	12.4	11.6	11.7
	Mean No. Liveborn Pups/Litter	12.4	11.6	11.7
	No. of Litters with Stillborn Pups	0	0	0
	Mean No. Pups Surviving to Lactation Day 4	12.3	11.5	11.7
	Mean No. Pups Surviving to Lactation Day 21	11.7	11.2	11.4
	No. of Total Litter Losses	0	0	0
	Mean Pup Body Weight at Birth (g)	1.6	1.6	1.6
	Mean Pup Body Weight at Weaning (g)	9.0	9.1	9.4
	Pup Sex Ratios (% males) at birth	54.8	51.7	50.2
	Pup Clinical Signs	-	-	-
	Pup Necropsy Observations	-	-	-
	Mean Concentration of cV1q in milk (µg/mL)	<0.2	0.4	7.5
	Mean Concentration of cV1q in sera (µg/mL)			
	LD 2	<0.2	11.5	40.8
	LD 15	<0.2	27.8	136.8
F₁ Males:	No. Evaluated Postweaning per Litter	25	25	25
(Postweaning)	No. Died or Sacrificed Moribund	1	1	0
	Clinical Observations	-	-	-
	Necropsy Observations	-	-	-
	Body Weight Change ^e (g)	25.8	26.3	26.1
	Preputial Separation	32.5	32.2	31.6
	Learning and Memory	-	-	-
	Mean No. Days Prior to Mating	3.2	3.4	2.6
	No. of Males that Mated/Copulation Rate ^f	95.8	95.6	100.0
	No. of Fertile Males/Fertility Rate ^f	100.0	95.4	100.0

^e From weaning to mating
^f Copulation rate = (no. of males that copulated/total no. of males on study) × 100; Fertility rate = (no. of males that sired offspring/total no. of males that copulated) × 100.
 - No noteworthy findings. LD = Lactation day

b(4)

Test Article: cV1q muG2a (b(4)) Anti-Mouse TNF Antibody

Effects on Pre- and Postnatal Development, Including Maternal Function				
Report Title: Intravenous Developmental and Perinatal/Postnatal Reproduction Toxicity Study of cV1q muG2a (b(4)) Anti-Mouse TNF Antibody in Mice, Including Postnatal Behavioral/Functional and Immunological Evaluations			Study No.: T-2001-002	
Dose (mg/kg)		0	10	40
F₁ Females:	No. Evaluated Postweaning	24	25	25
(Postweaning)	No. Died or Sacrificed Moribund	0	2	1
	Clinical Observations	-	-	-
	Necropsy Observations	-	-	-
	Premating Body Weight Change ^e (g)	18.9	18.6	19.4
	Gestation Body Weight Change (g)	35.1	33.3	31.9**
	Mean Age of Vaginal Patency (days)	32.0	31.2	30.8
	Learning and Memory	-	-	-
	Mean No. Days Prior to Mating	3.2	3.4	2.6
	No. of Females Mated	23	22	24
	No. of Pregnant Females	23	21	24
	Mean No. Corpora Lutea	15.9	15.5	15.0
	Mean No. Implantations	14.5	14.4	13.8
	Mean % Preimplantation Loss	7.9	6.8	7.3
	Humoral immune response	-	-	Decrease
F₁ Litters:	Mean No. Live Conceptuses/Litter	13.5	12.8	12.5
	Mean No. Early Resorptions	0.7	1.3	1.1
	Mean No. Late Resorptions	0.2	0.2	0.2
	Mean No. Total Resorptions	0.9	1.5	1.3
	No. of Litters with Dead Conceptuses	1	1	0
	Mean No. Dead Conceptuses	0.0	0.0	0.0
	Mean % Postimplantation Loss	6.3	10.7	10.0
	Fetal Body Weights (g)	1.31	1.34	1.33
	Fetal Sex Ratios (% males)	48.6	54.0	50.7
	Fetal Anomalies	-	-	-

^e From weaning to mating
 - No noteworthy findings
 Dunnett's Test ** - p<0.01

b(4)

Test Article: cV1q muG2a (b(4)) Anti-Mouse TNF Antibody

Effects on Pre- and Postnatal Development, Including Maternal Function						
Report Title: Intravenous Immunotoxicity Study of cV1q muG2a (cV1q) Anti-Mouse TNF Antibody in Mice					Test Article: cV1q muG2a (b(4)) Anti-Mouse TNF Antibody	
Design Similar to ICH 4.1.2? Yes	Duration of Dosing: Subset 1: G 6, 12 and 18 Subset 2: G 6, 12 and 18 and L 3, 9 and 15			Study No.: T-2003-013		
Species/Strain: CD-1® (ICR) BR mouse	Day of Mating: Day 0			Location in CTD: 4.2.3.5.3		
Age at First Dose: 80 days	Route: Intravenous			GLP Compliance: Yes		
Date of First Dose: 21 JAN 04	Vehicle/Formulation: 1 x Dulbecco's Phosphate Buffered Saline (DPBS) without Ca ⁺⁺ and Mg ⁺⁺ with 0.01% Tween® 80, pH 7.4					
Special Features: Milk and serum analysis and immunology analysis.						
No Observed Effect Level:						
F ₀ Females: > 40mg/kg/dose						
F ₁ Males: > 40 mg/kg/dose						
F ₁ Females: > 40 mg/kg/dose						
F ₀ Females:						
Dose (mg/kg)	0 (PBS) Subset 1	0 (PBS) Subset 2	40 (Control mAb) Subset 1	40 (Control mAb) Subset 2	40 (cV1q) Subset 1	40 (cV1q) Subset 2
No. of Animals						
No. Pregnant	14	15	10	9	10	9
No. Died or Sacrificed Moribund	1	0	0	1	1	1
No. Aborted or with Total Resorption of Litter	0	0	0	0	0	1
Clinical Observations	-	-	-	-	-	-
Gestation Body Weight (G 18)	53.9	55.9	-	-	-	-
Gestation Body Weight Gain (Gs 0 to 18)	+27.0	+29.0	-	-	-	-
Lactation Body Weight (LD 22)	38.8	37.7	-	-	-	-
Lactation Body Weight Gain (LDs 1 to 22)	+6.0	+6.4	-	-	-	-
Mean Duration of Gestation (days)	19.6	19.7	-	-	-	-
Necropsy Observations	-	-	-	-	-	-
Mean Concentration of cV1q in sera (µg/mL)						
Dam Lactation Day 15	0	0	0	0	0.1	609

For controls, group means are shown.
GD = Gestation day, LD = Lactation day
- No noteworthy findings

b(4)

Test Article: cV1q muG2a (b(4)) Anti-Mouse TNF Antibody

Effects on Pre- and Postnatal Development, Including Maternal Function						
Report Title: Intravenous Developmental and Perinatal/Postnatal Reproduction Toxicity Study of cV1q muG2a (cV1q) Anti-Mouse TNF Antibody in Mice, Including Postnatal Behavioral/Functional and Immunological Evaluations					Study No.: T-2003-013	
Daily Dose (mg/kg)	0 (PBS) Subset 1	0 (PBS) Subset 2	40 (Control mAb) Subset 1	40 (Control mAb) Subset 2	40 (cV1q) Subset 1	40 (cV1q) Subset 2
F ₁ Litters: No. of Litters Evaluated	14	15	10	9	10	9
Mean No. Pups/Litter	11.3	12.0	11.6	12.2	13.0	12.2
Mean No. Liveborn Pups/Litter	11.2	12.0	11.6	12.2	13.0	12.1
Mean No. of Stillborn Pups/Litter	0.1	0.0	0.0	0.0	0.0	0.1
Viability Index (Live pups Day 4/Day 1)	100	97.8	100	95.4**	94.8**	96.3**
Lactation Index (Live pups Day 21/Day 4)	98.1	98.3	94.8	84.8**	96.7	89.9**
Mean Pup Body Weight at Birth (g)	11.2	12.0	-	-	-	-
Pup Sex Ratios (% males) at birth	52.4	54.4	-	-	-	-
Pup Clinical Signs	-	-	-	-	-	-
Pup Necropsy Observations	-	-	-	-	-	-
Immunological Evaluations at 11 weeks of age	-	-	-	-	-	-
Immunological Evaluations at 22 weeks of age	-	-	-	-	-	-
Mean Concentration of cV1q in sera (µg/mL)						
Pup Lactation Day 2	0	0	0	0	137	128
Pup Lactation Day 15	0	0	0	0	73	443

For controls, group means are shown.
- No noteworthy findings
L = Lactation day. **p < 0.01

b(4)

Local Tolerance/Injection Site Studies in Monkeys

Local Tolerance

Test Article: Golimumab

Species/Strain Sex/No. Per Group	Route (Vehicle/Formulation)	Doses (mg/kg)	Noteworthy Findings	Study No./ Location in CTD
Cynomolgus Macaque 2 Males and 2 Females per Group	Subcutaneous and Intravenous (0.001% Tween 80, 0.01M sodium phosphate, 8.5% sucrose, pH6)	0, 10	Minimal: subcutaneous injection site erythema, edema and heat	T-2000-008 4.2.3.6
Cynomolgus Macaque 2 Males and 2 Females per Group	Subcutaneous (0.001% Tween 80, 0.01M sodium phosphate, 8.5% sucrose, pH6)	0, 10	Minimal – edema, erythema, heat, thickening Mild – chronic inflammation Mild – chronic vasculitis	T-2000-009 4.2.3.6
Cynomolgus Macaque 3 Male and 3 Females	Subcutaneous (0.001% Tween 80, 0.01M sodium phosphate, 8.5% sucrose, pH6)	50	Minimal – Mild: subcutaneous injection site erythema, edema, pain, heat and thickening	T-2001-007 4.2.3.6

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OVERALL CONCLUSIONS AND RECOMMENDATIONS

Introduction:

The nonclinical safety program for golimumab, a human monoclonal antibody that neutralizes the biological activity of human tumor necrosis factor alpha (TNF α), was designed by the applicant, Centocor Inc., in accordance with the ICH S6 guidelines (Guidance for Industry - Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals; ICH-S6 July 1997). Toxicology studies with golimumab were conducted in cynomolgus monkeys as golimumab was capable of neutralizing TNF α from several nonhuman primates including cynomolgus monkeys, but demonstrated little or no neutralization of dog, rabbit, mouse or rat TNF α . Therefore, the cynomolgus monkey was chosen as a pharmacologically relevant species for nonclinical safety evaluations.

The pivotal nonclinical studies in monkeys for golimumab include two 6-month chronic toxicology studies (SC and IV), an embryofetal development study (SC), and a pre- and post-natal development study (SC). Safety pharmacology endpoints were incorporated into intravenous (IV) and subcutaneous (SC) repeated dose toxicology studies conducted with golimumab in cynomolgus monkeys that also included neonatal assessments as part of the SC prenatal and postnatal reproductive toxicology study in monkeys. The safety pharmacology endpoints incorporated into these studies included measures of heart rate, blood pressure and electrocardiograms to assess cardiovascular safety, respiratory rate to assess respiratory safety and body temperature and daily clinical cage side observations to evaluate central nervous system safety. Studies of local tolerance/injection site effects in monkeys were also conducted. Additional supportive studies submitted, the results of which are to be used only in the product label, include chronic repeat dose toxicology studies and reproductive toxicology studies (fertility and early implantation, embryofetal development, and a pre- and post-natal development) in mice using an analogous anti-mouse TNF α mAb (cV1q) as submitted for the Centocor Inc. BLA 103,772 (Remicade®, infliximab) for the same indications.

Conclusions:

Product labeling for the TNF α inhibitor class of immunosuppressants (e.g., infliximab, etanercept, and adalimumab), most notable adverse reactions in patients receiving anti-TNF α therapy include serious and sometimes fatal blood disorders, infections (opportunistic infection in the form of tuberculosis and histoplasmosis), rare reports of lymphoma and solid tissue cancers, rare reports of serious liver injury, rare reports of drug induced lupus and rare reports of demyelinating central nervous system disorders (progressive multifocal leukoencephalopathy). No such effects were observed in the pivotal nonclinical studies submitted to support this application. The No Observed Adverse Effect Levels (NOAELs) in the pivotal nonclinical studies were the highest dose tested in those studies. Anticipated pharmacological actions of this immunosuppressive

drug and minimal local tolerance/injection site effects were observed at these NOAELs and were considered clinically monitorable and reversible.

In the pivotal repeat dose and reproductive toxicology studies in monkeys, at the highest dose tested (50 mg/kg SC twice weekly), no mortality or golimumab-related clinical signs of toxicity were observed during the dosing and post-dosing periods. No treatment-related effects were observed for the vast majority of biological indices evaluated that included body weight, food consumption, body temperature, physical examination, ECG, blood pressure, heart rate, ophthalmic evaluations, hematology, coagulation and serum chemistry parameters, urinalysis, immunotoxicity evaluations (lymphocyte subsets and Keyhole Limpet Hemocyanin ability to have an immune response analysis, organ weights, macroscopic, histopathologic or immunohistopathologic evaluations. No treatment-related effects were noted for any embryo-fetal or peri- and post-natal reproductive indices.

Notable, treatment related effects observed in the chronic SC monkey study was decreased IgG and IgM antibody responses to a KLH challenge as fewer animals in the golimumab dose groups mounted measurable antibody responses to KLH than in the control group. IgG antibody production was more affected than IgM antibody production with the most noticeable decline present in the 50 mg/kg dose group from day 41-69 with little to no response by day 92. In the chronic SC monkey study, reversible increases in B-lymphocytes were observed. Golimumab-treated animals were characterized as having an inconclusive immune response status because the lack of detection of an antibody response in all but a few low dose animals may have been compromised by high serum levels of golimumab. The systemic NOAEL was 50 mg/kg as only anticipated pharmacological effects and reversible and clinically monitorable local injection site effects (minimal irritation) occurred at 50 mg/kg.

Safety margins were calculated from the monkey studies based on blood levels (e.g., AUC and C_{max}). The proposed human dose is 50 mg SC every 4 weeks/monthly or ~1 mg/kg (0.71, 0.83, & 1 mg/kg for 70, 60, & 50 kg human, respectively) with associated blood levels of 75 µg•day/mL (AUC) and 1.71 µg/mL (mean steady state C_{max} for the pivotal human clinical trials of the 3 proposed medical indications).

SMs were considered adequate for human safety as animal:human comparisons as SMs were ≥ 75 for AUC-based SMs and ≥ 314 for blood level-based SMs. SMs of ≥ 1 are generally considered as adequate at this stage of nonclinical-based human safety assessment (i.e., post first in human dose). Based on this adequate SM criterion, the nonclinical data is considered supportive of human safety even though *in vitro* pharmacology studies showed that golimumab was up to 72-fold less potent at binding to and neutralizing the effects of cynomolgus TNF α than human TNF α as nonclinical levels were tested at levels in excess of proposed human levels and the highest nonclinical doses tested were the NOAELs.

The following table lists the SMs for the various studies using the appropriate dose comparisons:

Safety Margins ^a between Nonclinical Cynomolgus Monkey Study Doses and Proposed Human Doses for Golimumab							
Study type	Duration	Route ^b	NOAEL (mg/kg) ^c	Blood levels		Safety Margins ^d	
				AUC (µg•day/mL)	Cmax or highest value (µg/mL)	AUC-based	Blood level-based
Chronic	6 months	IV	50	11,635	2,627	155	1536
		SC	50	5657	2,459	75	1438
Embryo-fetal	Gestation	SC	50	27,051	1,613	361	943
Pre-/post-natal	2-generation	SC	50	NR ^e	1482 (parent)	NA ^f	867
				NR	537 (neonate)	NA	314
Local Tolerance/ Injection Site Effects	2x/week /3 weeks	SC	50	NR	795 ^g	NA	465

a – nonclinical No Observed Effect Level (NOAEL or blood level based) ÷ proposed human dose

b – intravenous (IV), subcutaneous (SC)

c – anticipated pharmacological action for systemic effects and minimal irritation at injection site for local effects

d - human dosing (mean AUC of 75 µg•day/mL based on FDA ClinPharm assessment of single dose data; median steady-state Cmax of 1.71 µg/mL following 50 mg every 4-week SC dosing in patients with RA, PsA, and AS)

e – not reported (NR)

f - not applicable (NA) for Safety Margins when no nonclinical AUCs reported

g – based on SC dosing at 2x/week for 3 weeks

The complementary mouse studies with the analogous anti-mouse TNFα mAb cV1q, as reported on the label, also indicated acceptable safety margins for reproductive toxicity and for chronic toxicity with suggestion that preneoplastic/neoplastic changes were not occurring after chronic dosing. No safety margins were calculated from mice studies as a surrogate/different drug was used.

Genotoxicity tests have not been conducted with golimumab. The range and type of genotoxicity studies routinely conducted for pharmaceutical drugs are not applicable to biopharmaceutical antibodies as noted in ICH S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.

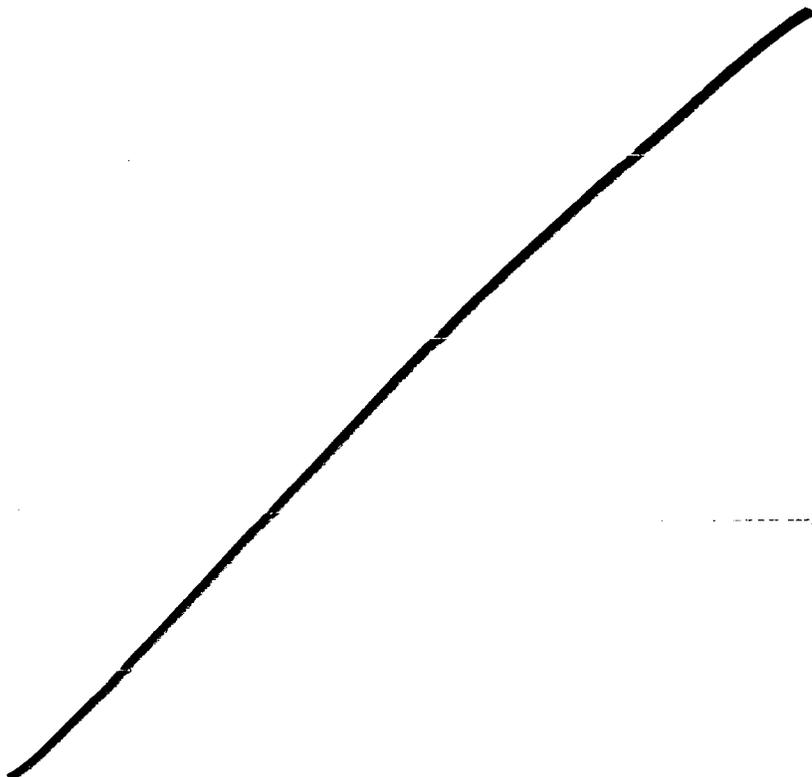
Carcinogenicity tests have not been conducted with golimumab. The carcinogenic potential of golimumab cannot be evaluated in standard 2-year bioassays in rodents because golimumab does not neutralize rodent TNFα. The carcinogenic potential of golimumab is being evaluated by monitoring of patients for Simponi® and other related

TNF α inhibitors. Preneoplastic/neoplastic lesions were assessed as part of chronic studies in monkeys and mice with no indications of any treatment-related preneoplastic/neoplastic lesions.

Unresolved toxicology issues: none

Recommendations: BLA approval is recommended.

Suggested labeling: suggested deletions with strikethrough and additions in red



b(4)

2 Page(s) Withheld

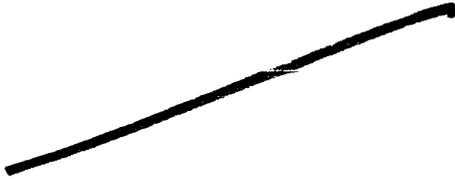
 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Withheld Track Number: Pharm/Tox-7



b(4)

Signatures (optional):

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

Supervisor Signature: Adam M. Wasserman, Ph.D. Concurrence Yes X No

APPENDIX/ATTACHMENTS - none

**Appears This Way
On Original**

PHARMACOLOGY/TOXICOLOGY BLA FILEABILITY CHECKLIST
Division of Anesthesia, Analgesia, and Rheumatology Products

BLA Number: 125,289

Applicant: Centocor, Inc.

Stamp Date: June 24, 2008

Drug Name: Golimumab (Simponi)

IS THE PHARM/TOX SECTION OF THE APPLICATION FILEABLE? Yes [X] No []

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameters	Yes	No	Comment
1	On its face, is the Pharmacology/Toxicology section of the BLA organized in a manner to allow substantive review to begin?	X		
2	Is the Pharmacology/Toxicology section of the BLA indexed and paginated in a manner to allow substantive review to begin?	X		
3	On its face, is the Pharmacology/Toxicology section of the BLA legible so that substantive review can begin?	X		
4	Are final reports of ALL required* and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility*, juvenile studies, ocular toxicity studies*, acute adult studies*, chronic adult studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetic studies, etc)? Have electronic files of the carcinogenicity studies been submitted for statistical review?	X		
5	If the formulation to be marketed is different from that used in the toxicology studies, has the sponsor made an appropriate effort to either repeat the studies with the to be marketed product or to explain why such repetition should not be required?	X		
6	Are the proposed labeling sections relative to pharmacology appropriate (including human dose multiples expressed in mg/m ² or comparative serum/plasma levels) and in accordance with 201.57?	X		
7	For a 505(b)(2) submission, has the sponsor identified a referenced product?			NA
8	For a 505(b)(2) submission, has the sponsor submitted patent certification information to support the information referenced in the proposed drug product labeling?			NA
9	Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions?	X		
10	Based upon a cursory review, do the excipients appear to have been adequately qualified?	X		Potential outstanding issue is submicroscopic  particles/droplets in drug product to be addressed by the Quality Reviewer at this stage.
11	Has the applicant submitted any studies or data to address any impurity or extractable issues (if any)?		X	
12	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted a rationale to justify the alternative route?	X		
13	Has the sponsor submitted a statement(s) that all of the pivotal pharm/tox studies been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any	X		

b(4)

	significant deviations?			
14	Has the sponsor submitted a statement(s) that the pharm/tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns?	X		
15	From a pharmacology perspective, is this BLA fileable? If "no", please state below why it is not.	X		FILING ISSUES: none
16	If the BLA is fileable, are there any filing review issues that need to be conveyed to Sponsor? If so, specify:		N	Filing review issues for the 74-day letter: none

Reviewing Pharmacologist: Gary P. Bond August 11, 2008
 Gary P. Bond, Ph.D. date

Supervisory Pharmacologist: Adam M. Wasserman 8/12/08
 Adam M. Wasserman, Ph.D. date