2.6.6 TOXICOLOGY

2.6.6.1 Overall Toxicology Summary

Single Dose Toxicology

No studies were conducted specifically to evaluate single dose ACZ885 toxicology. First dose observations in the repeated dose study methodologies provided information on potential acute treatment-related toxicity, in addition to the observations throughout the dosing and recovery periods in the repeat-dose studies in marmosets. The findings in the first-dose observations, if any, are summarized within the context of the repeat-dose toxicity summary, below.

Repeated Dose Toxicology

Repeated dose IV toxicology studies of 4-weeks and 26-weeks duration, and SC toxicology studies of 43-days and 13-weeks duration were conducted in marmosets, the only species tested which shows full cross-reactivity with that in humans.

Marmosets (n=5/sex/control and high dose [HD], 3/sex/low dose [LD] and mid-dose [MD]) were administered ACZ885 by slow bolus IV injection at doses of 0, 10 (LD), 30 (MD), and 100 (HD) mg/kg twice weekly for 4 weeks, for a total of 8 infusions. The observations included standard toxicology parameters throughout the dosing period, such as toxicokinetic, ophthalmoscopic, electrocardiographic (ECG), and histopathology measures. Additionally, anti-ACZ885 antibody analyses were conducted using sheep anti-ACZ885 serum as the positive control, and pre-treatment serum for the negative control. Lymphocyte (CD3, CD4, CD8, CD14, CD16, CD20, CD56) subpopulations and monocytes were immunophenotyped using flow cytometry. Additional groups were given vehicle control and HD ACZ885 (n=2/sex/group) and were evaluated for 2 months following the 4-week treatment period for reversibility of any treatment-related effects found, and for potential delayed treatment-related toxicity. The results showed no treatment-related effects at any dose level, during the dosing and recovery periods. No anti-ACZ885 antibodies were found, and there were no treatment-related findings in the immunophenotyping of lymphocyte subpopulations and monocytes, although there was considerable within-group and within-subject variability, with increases and decreases in specific lymphocyte subpopulations. Total leucocyte counts were also highly variable within and across groups and sexes (increased and decreased) during the study.

No treatment-related effects were observed in a chronic toxicology study (Study #038070) in marmosets (n=4/sex/dose main study and 2/sex/control and high dose (HD) for 6-week reversibility/recovery evaluation) administered ACZ885 by IV bolus injection at doses of 0, 10 (LD), 30 (MD), and 100 (HD) mg/kg, twice weekly for 6 consecutive months. Standard toxicology parameters, lymphocyte and monocyte immunophenotyping, and anti-ACZ885 antibody evaluations were performed as in the 4-week IV study in marmosets, described above. Additionally, semen was collected from the male marmosets for sperm evaluation (motility, number, and morphology), testicular

size was measured, testicular tissue was examined microscopically for testicular cell population quantitation, and serum testosterone was measured. No treatment-related effects were observed on the standard toxicology parameters, male reproductive system, and on lymphocyte subpopulations and monocytes during the 6-month dosing and 6-week recovery periods. No anti-ACZ885 antibodies were detected.

A preliminary, 43-day SC toxicity/tolerability study (Study #0370163) was conducted in female marmosets for dose-selection in the subsequent 13-week SC toxicity studies. The marmosets (n=2F/control and 4F/dose) were each administered two doses of ACZ885 at 0 (vehicle control), 5 (LD), 50 (MD), and 150 (HD) mg/kg, 43 days apart. Standard toxicology parameters, except for ophthalmoscopic examinations and ECG analyses were evaluated. Anti-ACZ885 antibody formation was assessed on Day 43. No recovery groups were included in this study. One MDF showed anemia on Day 44 with decreased red blood cells, hemoglobin and hematocrit, and inflammatory leukocytosis with increased lymphocytes, monocytes and eosinophils. Histopathology findings in this study included slight hyperplasia in the jejunum (epithelial and Peyer's patch) with marked lymphocytic infiltrate and minimal abscess in 1 HDF, slight leukocytic infiltrate in 1 MDF and 1 HDF, slight (1 HDF), and minimal to moderate (1 control, 3 LDF, 2 MDF, and 3 HDF) hepatocellular vacuolation. The findings were not observed in the longer-term SC and IV toxicity studies in marmosets. Etiology secondary to possible ACZ885-induced effects on immune function cannot be ruled out, however.

In the first 13-week SC toxicology study (Study # 0470033), male (M) and female (F) marmosets (n=4/sex/dose) were administered ACZ885 at the doses of 0 (vehicle control), 15 (LD), 50 (MD), and 150 (HD) mg/kg/twice weekly for 13 consecutive weeks. Additional marmosets (2 control and 2 HD recovery animals) were evaluated for 8 weeks after the end of the dosing period, to evaluate reversibility of any adverse treatment-related effects and to detect possible delayed emergence of treatment-related toxicity. Standard toxicology parameters were evaluated throughout dosing and recovery, such as clinical signs, ophthalmoscopy, ECG (baseline and Week 13), clinical laboratory examinations, necroscopic evaluation (organ weights, gross and microscopic examinations), and toxicokinetics (TK). Additionally, serum testosterone was analyzed (at baseline, Treatment Week 13 and Recovery Week 8), and blood samples were analyzed for immunophenotyping of peripheral blood leukocytes (CD20, CD3, CD4, CD8, CD16, CD4:CD8, CD3:CD20) and splenic nucleated cell suspension (CD20, CD3, CD4, CD8, CD4:CD8, CD3:CD20), anti-ACZ885 antibody determination, and gene expression analysis. Gene expression was also analyzed in tissue samples from liver, kidney, spleen, lung, and mesenteric lymph nodes. The results showed minimal leukocytic or mononuclear infiltrates at the injection site, without a relationship to dose. The histopathology examination also revealed a dose-related increase in minimal lymphoid hyperplasia of the spleen (0 control, 1 LD [minimal], 2 MD [slight], and 3HD [2 minimal, 1 slight]), in large active follicles in the Treatment and Recovery M. A relationship to ACZ885 treatment to the findings in spleen cannot be ruled out, particularly since the incidence of the effects were increased in a dose-related manner and the severity was slightly increased from minimal to slight at the MD and HD. However, the effects in spleen in the M were found in the absence of any treatment-related effects

on phenotyping of splenic suspensions and blood samples, and on anti-drug antibody levels. Also, there were no treatment-related splenic findings in the F marmosets, including functional, gross and microscopic effects. The findings in spleen were not reproducible; no treatment-related splenic hyperplasia were observed in the other toxicology studies in marmosets, including the longer duration 6-month IV toxicity study. Finally, no evidence was found for anti-ACZ885 antibody formation at any dose in the M and F. The Applicant monitored spleen size in clinical study CACZ8852201, without detecting a treatment-related effect. For these reasons, the findings in spleen in the M in this study only, are noted but less compelling indication of a target organ by ACZ885, and not of great concern. A NOAEL for target organ toxicity can be considered to be the highest dose evaluated (150 mg/kg/twice weekly). The exposure at this dose ($AUC_{0\text{-}1368h}$ = 462,113 (M) – 342,748 (F) mcg.h/ml (mean 402,430 mcg.h/ml), represents approximately 24 times the clinical exposure ($AUC_{0\text{-}inf}$) of approximately 17,000 mcg.h/ml at the dose of 150 mg given once every 8 weeks in adult CAPS patients, on an AUC basis, and 70 times based on body weight (mg/kg).

A second 13-week SC toxicology study (Study # 0770370) was conducted in marmosets to compare the ACZ885 TK and toxicity profiles of Batch A (ACZ885 lyophilisates made from the —— and intended for marketing) and Batch B (ACZ885 lyophilisates produced using the ——— and evaluated in the earlier nonclinical toxicology studies). The designations of Batches "A" and "B" in this study had no relationship to the designations of "Product A" or "Process A" (—— and "Product B" or "Process B" (——— , previously discussed in this review, above. In this study, male (M) and female (F) marmosets (n=4/sex/dose group, no recovery groups evaluated) were administered 0 (vehicle control) or 150 mg/kg/twice weekly ACZ885 from the Formulation A (Batch A, ———) or Formulation B (Batch B, ——— for 13 consecutive weeks. Standard toxicology evaluations, such as clinical signs, clinical pathology, ophthalmology, and necroscopy, but not electrocardiography and urinalyses, were performed. Anti-ACZ885 antibody determination was conducted. There were 2 deaths in M cagemates given Formulation B ——— , on Treatment Days 57 (euthanized) and 72 (found dead). One of the decedents (euthanized on Day 57) showed clinical chemistry changes (increased serum urea, creatinine, and phosphorus concentration with mild-moderate increased glucose, cholesterol and triglycerides, and decreased sodium, potassium and chloride concentrations), and enlarged testes without histopathology correlates. The histopathology examination in that animal showed mixed inflammatory cell infiltration and ulceration in the intestinal mucosa, with neutrophil loss and blood in the lumen, and neutrophilic inflammation with bacteria throughout the body. The death was attributed to septicemia secondary to intestinal ulceration. The cagemate found dead on Day 72 showed marked thymus lymphoid depletion. The cause of the death on Day 72 was not determined, but a relationship to treatment cannot be ruled out. Fecal changes (diarrhea, mucoid feces) were observed in 75%-100% M given Formulation B ——— and 50%-75% F given Formulation A ——— Body weight loss, observed in all groups including controls, was higher in the M given Formulation B ——— than in the other groups. Decreased serum albumin (mild-moderate) was found in 3/4 M and 1/4 F given Formulation B ———) compared to baseline and controls. There were

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no treatment-related effects in the histopathology examination in the animals that survived to the end of the study. The NOAEL in this study can be considered to be 150 mg/kg for the Formulation A ———), but was not determined for Formulation B ——— , due to increased body weight loss and decreased serum album in 3/4 M and 1/4 females and the deaths in 2 males, attributed to septicemia in one, and of ndetermined cause in the other marmoset showing thymic lymphoid depletion. There was no evidence of anti-ACZ885 antibody response in any group, and no differences in exposure between the two Batches in the marmoset TK analysis. Overall, treatment-related toxicity appears to have been considerably higher in frequency and severity in the marmosets administered the original Formulation B ACZ885 produced by the ——— and used in previous nonclinical toxicology studies, than in the marmosets administered ACZ885 produced using the ——— that is intended for marketing. Also, it should be noted that septicemia secondary to intestinal ulceration has been observed in historical control marmosets. b(4) b(4)

Genetic Toxicology and Carcinogenicity

Studies to evaluate ACZ885 genetic toxicology and carcinogenicity were not requested by the Agency, and were not conducted. These studies are generally not required for biologic drugs unless there is evidence based on the primary and secondary pharmacology profiles, mechanism of action, or findings in the general toxicology studies that raise concerns regarding genotoxic and/or carcinogenic potential.

Reproductive and Developmental Toxicology

A full battery of reproductive toxicology studies was conducted by the Applicant, including evaluations of fertility (Segment I) in mice, embryo-fetal development (Segment II) in mice and marmosets, and pre- and post-natal development (Segment III) in mice. The studies in mice used 01BSUR, because ACZ885 does not cross-react with any of the recombinant murine IL-1 $_{B}$ isoforms due to differences in the amino acid position 64 of IL-1β, which consists of glutamic acid in humans and marmoset monkeys and alanine in the other species. As previously discussed in this review, the surrogate antibody was produced in mice immunized with recombinant mouse IL-1β (mouse IgG1/κ isotype which has no interaction with Fcγ receptors, converted to IgG2a/κ isotype which is functionally equivalent to the human IgG1 isotype in binding to Fcγ receptors). 01BSUR binds to the IgG1 and IgG2a isotypes of mouse IL-1β. The 01BSUR pharmacokinetic and toxicokinetic profiles were shown to be comparable to those of ACZ885 in the studies and comparisons conducted for the pharmacokinetic program during drug development.

To explore potential ACZ885 effects on fertility (Study 0680149), male and female CD1 mice (n=22/sex/dose) were administered 01BSUR by subcutaneous (SC) injections at the doses of 0 (vehicle control), 15 (LD), 50 (MD), and 150 (HD) mg/kg, once weekly from 4 weeks before mating through the end of mating in the male (M) mice, and from 2

weeks before mating through Gestation Day (GD) 3 or 4 in the female (F) mice. The doses were selected based on multiples of the anticipated maximum recommended human dose (MRHD), on the results of prior toxicology studies in mice, and on feasibility limitations of the test article, such as solubility and injection volume. Same-dose M and F mice were cage-paired for up to 15 days. The F were examined daily for evidence of pregnancy using the appearance of a vaginal copulatory plug. In-life parameters evaluated in all F_0 M and F included mortality, clinical signs, body weights, food consumption, estrous cycles (F only) and serum 01BSUR levels. Necropsy was performed 3 weeks after the end of mating in the M and on GD 13 in the F, and included gross pathology and organ weights. Histopathology examinations of all reproductive organs and tissues were performed, with additional examination of abnormal tissues in the single decedent in the study. The M reproductive assessments were sperm motility, spermatozoa counts and morphology, and histopathology of the right testis. Parental mating performance (mating index, fertility index, and conception rate) and uterine data (preimplantion and post implantation losses) were calculated based on the results of the necroscopic examinations. One HDF was found dead on Mating Day 2, with no prior clinical signs of treatment-related toxicity, but which showed stomach and duodenal hemorrhage in the necroscopic examination, unlikely to be related to treatment. There were no treatment-related effects on in-life parameters, parental mating performance and fertility parameters (mean days to mating, mating and fertility indices, and conception rate), and in the uterine examinations (numbers of corpora lutea, implantation sites, live/dead fetuses, resorptions, and pre- and post-implantation losses). No treatment-related effects were found in the necroscopy evaluations, with the exception of spleen enlargement in all female groups including controls, that is considered to be possibly related to the vehicle (sucrose, L-histidine, Tween 20), in agreement with the Applicant. No treatment-related changes in sperm motility, and spermatozoa counts and morphology were found. In conclusion, there was no evidence of treatment-related effects on fertility and early embryonic development in CD-1 mice administered 01BSUR at doses of up to 150 mg/kg by SC injection once weekly.

A study was conducted to evaluate potential ACZ885 effects on embryo-fetal development (Segment II Study # 0680148) in CD-1 mice. Pregnant, female (F) mice (n=22/dose) were administered 01BSUR at subcutaneous (SC) doses of 0 (vehicle control), 15 (LD), 50 (MD), and 150 (HD) mg/kg on gestation days (GD) 6, 11, and 17. Satellite groups (n=3 dams/dose) were used for the toxicokinetic (TK) analyses. The parameters evaluated in the F_0 dams included in-life examinations (standard mortality, clinical signs, body weights, and food consumption) and pathology following the GD 18 euthanasia (internal and external gross examinations), with examinations for pregnancy status, numbers of corpora lutea, uterus weights and contents (including placentas, numbers and positions of live and dead fetuses, early, middle and late resorptions, and implantation sites. The fetuses were removed at necropsy (GD18) and examined for body weights, sex, and detailed external and internal examinations were performed, including microscopic evaluation for major and minor visceral and skeletal malformations and variations. Pregnancy rate, pre- and post-implantation loss, and sex ratio were calculated. Full TK analyses were conducted in the dams, and the fetuses were assessed for drug exposure via placental transfer following the last maternal dose (144h

post-dose). The results showed no maternal toxicity in the in-life observations and necroscopic examination. There were no treatment-related effects on pregnancy rates, corpora lutea, implantation sites, live and dead fetuses, sex ratio, resorptions, and pre- and post-implantation loss. The fetal examinations showed no treatment-related effects on fetal weights, major external, visceral or skeletal malformations, and external and visceral variations or anomalies. However, treatment-related developmental delay was suggested at the MD and HD in the absence of maternal toxicity, by an increased incidence of incomplete ossification of the parietal bones at 50 (11.3%, 14/124 fetuses in 9/20 litters) and 150 (24%, 25/104 fetuses in 8/18 litters) mg/kg when compared to the concurrent controls (2.8%, 3/106 fetuses in 1/17 litters) and to the historical controls for the laboratory (0%-4.2%). Additionally, the fetal examinations revealed incomplete ossification of the frontal bones at 150 mg/kg, representing 18.3% (19/104 fetuses in 9/18 litters) compared to 5.7% (6/106 fetuses in 3/17 litters) in the concurrent controls and 0%-4.2% in the historical controls for the laboratory. There were no other treatment-related skeletal or other findings in the fetuses. The results of the TK analyses showed adequate 01BSUR exposure in the dams (serum concentration at the HD = 321 mcg/ml) and support for placental transfer and adequate exposure in the fetuses, with a mean fetal serum concentration of 136 mcg/ml at the HD on Day 17. An apparent decrease in exposure from GD6 to GD17 in the dams likely reflects differences in data collection timepoints on GD6 (120h after dosing) and GD17 (24h after dosing), and the rate of systemic absorption following SC injection. The results of this study provided no evidence for major malformations/teratogenicity by the 01BSUR.

A second embryo-fetal development (Segment II) study was conducted in marmosets (Study # 0480152). Pregnant female (F, n=17 controls and 18/dose) marmosets were administered ACZ885 by SC injection at the doses of 0 (vehicle control), 15 (LD), 50 (MD), and 150 (HD) mg/kg twice weekly (3-4 days apart) on gestation days (GD) 25-109. The doses were selected based on 1.5X, 5X and 15X the estimated maximum recommended human dose (MRHD) and on the results of a 13-week SC toxicity study on ACZ885 in marmosets (Study # 1470033). Standard maternal in-life parameter evaluations (mortality, clinical signs, pregnancy confirmation, body weights, and food consumption) and Cesarean section procedures (GD112-114) were conducted, but no necroscopic evaluations of the dams were performed, because no dams were found moribund or dead. Following Cesarean section, the fetal examinations included placental and fetal weights, numbers of dead and live fetuses, sex, body measurements (such as distances from coccyx to cranium, tip of nose to os occipitale, from os frontale to os occipitale, width of head, and distance between eyes), external macroscopic and microscopic examinations, and external defect examinations (such as symmetry of head, facial form, extremities, and genitals). Full internal necropsy was performed on all fetuses, and included gross examinations, organ weights, and microscopic examinations of most internal organs (for the complete list of organs examined, see full review under Reproductive and Developmental Toxicology, above). The fetal skeletons were examined for major and minor malformations and variations. Blood and amniotic fluid were sampled at the time of Caesarean section for TK analyses in the maternal (weekly) and fetal marmosets (umbilical cord and fetus at Caesarean section). Anti-ACZ885 antibody formation was evaluated on the day of Caesarean section. The results of this

study showed no maternal toxicity by ACZ885 at any dose. There were slight decreases in placental weights (mean of 6.7 g) at the HD compared to control placental weights (mean of 8.6 g), that is probably due to the lower litter size (HD mean 1.86 vs. 2.45 in the controls) at this dose. Ultrasonography demonstrated no decreases in the numbers of fetuses vs. the numbers of embryos present at Day 50, and therefore the reduced litter size was probably not a result of resorptions. Early resorptions could not be assessed because uterine scars are not formed in marmosets upon early abortion. There was a slight increase in numbers of fetuses with kinked (3 HD vs. 1 control) and/or bent (1 at the HD vs. 0 in the controls) tail end in the external examination. No treatment-related visceral variations or malformations were found. The skeletal examination revealed a slight increase in zygostyle (incomplete vertebral ossification) in 1, 4, 10, and 2 fetuses in the control, LD, MD, and HD groups, respectively, and misaligned and/or bipartite in 5, 17, 16, and 12 in the control, LD, MD, and HD groups respectively in all treated groups. The histopathology examination of fetal organs found no treatment-related effects. The results of the TK analyses showed adequate maternal exposure to the test article, that increased with dosing duration, reflecting accumulation. All fetuses of the treated dams were exposed to ACZ885 in a dose-proportional manner. The test article was found in fetal serum and amniotic fluid at concentrations of 7.0%-8.7% and 1.8%-2.0%, respectively, the concentrations in maternal serum. No anti-ACZ885 antibody formation was detected in the maternal and fetal marmosets. The results of this study showed no evidence of major malformations/teratogenicity by ACZ885 in marmosets, although there was some evidence of a slight treatment-related developmental delay, indicated by slightly increased incidence of bent/kinked tail at the HD in several fetuses and increased incidence of incomplete vertebral ossification at all ACZ885 doses. The results also suggested a slight treatment-related reduction in reproductive performance indicated by slight reductions in the numbers of fetuses per litter and reduced placental weights at the HD.

A pre- and post-natal development study (Segment III) was conducted in CD-1 mice (Study # 0680150). Pregnant mice (n=25F/dose, F_0 generation) were administered 01BSUR by SC injection at the doses of 0 (control vehicle), 15 (LD), 50 (MD), and 150 (HD) mg/kg once weekly on gestation days (GD) 6 and13, and on post partum days (PPD) 2, 9, and 16. The F_1 generation pups were culled to 4/sex/dose group on PPD 4, for pup evaluation, and to 25/sex/dose for adult F_1 evaluation. Additional F_1 groups were investigated for immunogenicity (10/sex/dose) and immunology (10/sex/dose). F_0 (maternal) in-life parameters examined were mortality, clinical signs, body weights, food consumption and reproductive parameters addressing treatment-related effects on gestation, parturition, and lactation (gestation index, length of gestation, duration of parturition, numbers of live, dead and malformed pups, implantation scars, live birth index, and rates of pregnancy, mating index, and conception rate). Maternal gross pathology was performed on PPD 7. F_1 pup and adult physical development was examined, and included measures of viability and survival throughout lactation, clinical observations, malformations, physical development (pinna unfolding, eye opening), reflex development (righting reflex and auricular startle response) and gross pathology in the pups, and survival, clinical signs, body weights, physical development (vaginal opening, preputial separation, visual placing and papillary closure), organ weights and

gross and microscopic examinations of the major organs, injection sites, and abnormalities. The F_1 behavioral evaluation addressed motor activity (PPD 35 and 60), startle habituation (PPD 55), and passive avoidance (PPD 64). Mated F_1 females (F) were evaluated for reproductive performance, such as estrous cycle, days to mating, length of gestation, and duration of partuirition. The immunology assessment was conducted in blood, thymus and spleen, using immunophenotyping to determine the total, absolute and percent differential counts for T, Helper T, Cytotoxic T, B, and Natural Killer lymphocytes in the F_1 offspring at necropsy on PPD 79. The F_2 generation measures included sex ratio, numbers of live and dead pups, and malformed pups at birth, and the F2 pups were examined for body weights, sex, numbers of live and dead, viability, clinical observations (throughout lactation) and external and internal malformations and variations. 01BSUR antibody formation was tested in the F_0 and F_1 generations on PPD 7.

Two HD dams were found dead on PPD 13 and 17. No clinical signs were observed in the decedents, but histopathology examination showed splenic enlargement and lymphoid hyperplasia in both dams, pale discoloration of the spleen in one, and liver enlargement in the other dam, with increased extramedullary hematopoiesis. There were no treatment-related in-life and gross pathology effects in the F_0 dams that survived to the end of the study. No treatment-related effects on physical development and gross pathology were observed in the F_1 Pups and F_1 Adults. Additionally, there were no treatment-related effects in the behavioral evaluation of motor activity, startle habituation, and passive avoidance, in F_1 reproductive parameters, and in the F_1 immunology assessment of blood, thymus, and spleen, including effects on weights, immunophenotyping data, lymphocyte subsets, and macroscopic and microscopic examinations, except for increased histiocytosis in the mesenteric lymph nodes. The histopathology examination of the F_1 adults showed a treatment-related increase in the incidence of histiocytosis in the mandibular and mesenteric lymph nodes at the MD (3/9 vs. 0/10 controls and 4/9 vs. 2/10 in the controls, respectively) and HD (2/10 vs. 0/10 controls and 3/10 vs. 2/10 in the controls, respectively) in the M. No anti- 01BSUR antibodies were found in the adult F_1 mice, and there were no treatment-related effects in the F_2 generation evaluations, including the external and internal examinations. The TK analyses showed 01BSUR levels in the F_1 pups at levels of 6 times higher than in the F_0 generation dams, and also detected 01BSUR in the F_1 adults, although at lower levels. In conclusions, the results of this study found no 01BSUR-related effects on pre- and post-natal development, although there was evidence of potential toxicity in spleen in the 2 F_0 dams that were found dead, and lymph nodes in the F_1 offspring.

Juvenile Toxicity

The Applicant conducted a study in juvenile CD-1 mice using 01BSUR, in support of the safety of a canakinumab indication for administration to pediatric patients ages ≥ 4 years and above (Study # 0770274). The juvenile study was performed in agreement with Agency recommendations (see meeting minutes for October 21, 2008 pre-BLA meeting with the Applicant). 01BSUR was administered to the juvenile mice (n=20/sex/group) by

SC injection at doses of 0 (control vehicle), 0 (untreated control), 15 (LD), 50 (MD), and 150 (HD) mg/kg/once weekly on post partum days (PPD) 7-70 (total 9 injections). Additional satellite groups of juvenile mice were used in evaluations of 4-week post-treatment phase drug-free reversibility, toxicology (n=20/sex/group), 1-day toxicokinetics (TK) (n=12/sex controls and 60/sex/treated group), 3-week main study immunology (n=10/sex/group), and 9-week dosing phase + 4-week recovery phase immunology (n=10/sex/group). The pups were observed daily for mortality and clinical signs, and twice weekly for body weights and food consumption. Physical development was evaluated throughout development in the pre-weaning (eye opening, auricular startle, PPD10) and post-weaning (vaginal opening, preputial separation, PPD 21 until end of study) periods. Behavioral performance was measured using motor activity (PPD 13), auditory startle habituation (PPD 55), and passive avoidance (PP Week 14, recovery animals). The fertility assessments, such as mating and uterine examinations for numbers of corpora lutea, live/dead embryos, and resorptions were conducted in the recovery females (F) mated with same-dose recovery males (M), ages 14-15 weeks. Additionally, standard toxicology parameters, such as clinical pathology, organ weights, comprehensive macroscopic and microscopic examinations, as well as TK parameters were evaluated. Immunogenicity (predose and at termination) and immunology assessments using immunophenotyping in blood, spleen and thymus were conducted for measurement of Total, Helper, Cytotoxic, Double negative, and Double positive T cells, B cells and Natural Killer cells. The results showed a slight increase in the mean day of development of auricular startle in the pre-weaning MDM and HD M and F compared to concurrent controls. However, the values observed were similar to control values in Study # 901098, and there were no treatment-related effects in the post-weaning evaluation of auditory startle habituation. There was a statistically significant delay in the mean day to vaginal opening at the HD (28.5 d) compared to controls (26.28 d), but the values were within historical control range for the performing laboratory (25.7-29.7 d). In the fertility assessment, there was a statistically significant increase in pre-implantation loss at the HD (20.38%) compared to controls (4.26%), predominantly due to a loss in 1 dam of 71.4% litter. However, the mean number of live embryos in the HD group (12.8) was within the historical range of 11.6-13.0 for the laboratory. Treatment-related inflammation observed at the injection site in the M and F during the dosing period was reversed during the recovery period. There were no treatment-related effects in the evaluation of immunogenicity and in the immunophenotyping in blood, spleen and thymus, on lymphocyte and lymphocyte subset counts. The results of the TK analyses showed a dose-proportional increase in exposure ($AUC_{0.083h-168h}$ and C_{max}) and 6-fold increase in exposure from PPD7 to PPD63, suggesting accumulation. Although a relationship to treatment of the juvenile development effects observed in this study, including delayed vaginal opening, increased mean day of auricular startle development, and increased pre-implantation loss cannot be entirely ruled out, the effects are not considered to be of major concern because the findings are within historical range, there were no treatment-related effects in corresponding measures of toxicity, and/or the incidence of the findings in only 1 mouse (loss of litter).

Immunotoxicity

Potential ACZ885 immunotoxicity was investigated specifically in a 28-day weekly SC injection study in Albino mice (Study #301461). The CD-1 mice (n=20/sex/group) were administered 01BSUR at doses of 0 (vehicle control), 10 (LD), 50 (MD), and 150 (HD) mg/kg/once weekly on Study Days 1, 8, 15, 21, and 28. Satellite groups included additional 20 mice/sex/group for a 28-day reversibility phase (10/sex/dose for assessment of T-cell Dependent Antibody Response (TDAR)/immunogenicity cohort, and 10/sex/group for assement of immunophenotyping, immunogenicity, and toxicokinetics). The immunizing agent (Imject Mariculture Keyhole Limpet Hemocyanin [KLH], 200 mcg/ml, 0.5 ml/animal) was administered by IP injection on Study Days 15 and 22 in the main study animals, and on Days 42 and 49 in the recovery animals. The observations also included clinical signs, body weights and food consumption. Immunophenotyping was performed on Day 29 in the main study animals and Day 57 in the recovery animals. Blood samples, spleen tissue and thymus tissue were typed as relative proportions and absolute numbers of Total ($CD3e^+$), Helper ($CDe3^+/CD4^+$), and Cytotoxic ($CDe3^+/CD8a^+$) T lymphocytes, Double positive T lymphocytes (spleen and thymus, $CD3e^+/CD4^+/CD8a^+$), Double negative T lymphocytes (spleen and thymus, $CD3e^+/CD4^-/CD8a^-$), B lymphocytes ($CD19^+$), and Natural Killer lymphocytes ($CDe3^-/NK1.1^+$). Anti-01BSUR antibody formation was assessed in the main TDAR/immunogenicity animals and recovery (immuonphenotyping, immunogenicity, and TK corhorts). TDA and T-cell dependent antigen IgM and IgG antibody responses were analyzed following the IP KLH injections on Days 15 and 22. Additionally, detailed gross pathology, organ weights (brain, spleen, and thymus) and microscopic examination of the lymph nodes (mandibular, unilateral, inguinal, bilateral, and mesenteric, spleen, and thymus were conducted on the main and recovery animals. The results showed no treatment-related effects on immunophenotyping and on the mean absolute and relative percentages of lymphocytes in blood, spleen and thymus. No anti-drug antibody was found. There was an apparent treatment-related inhibition of anti-KLH IgG response (up to 61% at the MD and HD) that is considered to be related to an abnormally high response in 2 control M. On the other hand, an increased anti-KLH IgG response was observed in the treated F, that is attributed to extremely high variability. There were no treatment-related changes in the anti-KLH IgG response in the recovery animals and no anti-KLH IgM response in any group. Slight increases noted in absolute and relative thymus weights in the main study F at ≥50 mg/kg/wk vs. controls, was not statistically significant, and were without macroscopic and histopathology correlates, not found in the recovery animals, and therefore unlikely related to treatment. In conclusion, 01BSUR was negative for inducing immunotoxicity in the CD-1 mouse at doses of up to 150 mg/kg/week for 4 weeks under the conditions of this study.

Local (Intra-articular) Tolerance

A single-dose, intra-articular ACZ885 study was conducted in marmosets to investigate potential local toxicity (Study # 1939-018). Three female (F) marmosets received ACZ885 injections at 0 (control placebo) in the left knee joint, or 10 mg/kg (57.6 mg/ml in 0.2 ml/kg, maximum feasible dose) in the right knee joint, followed by a 3-day post-dose evaluation period. The measurements included a limited set of standard toxicology

parameters, and included clinical signs, body weights, hematology, organ weights, and macroscopic and microscopic examination of the knee joints with surrounding tissues in both knees, as well as in popliteal and inguinal lymph nodes. A full histopathology battery examination was conducted in animals showing possible treatment-related effects in the gross necropsy assessment. The results of the study showed ataxia in the hindlimbs in one marmoset. Treatment-related decreased lymphocytes (mean 41% vs. 64% at baseline) and increased neutrophils (mean 58% vs. 35% at baseline) were found in the both ACZ885-treated groups. The gross pathology examination revealed enlarged/mottled adrenals and kidneys in one, and swollen right finger with subcutaneous abscesses, ileal invagination, and red discolored urinary bladder in another marmoset. The animal with enlarged adrenals and kidneys was examined histologically and showed moderate cortical hypertrophy in the adrenals, moderate inflammatory cell foci, and slight fibrosis with slight atrophic tubuli in the kidneys. The marmoset with red discolored urinary bladder in the gross pathology examination, showed marked acute inflammation and ulceration of the urinary bladder upon microscopic evaluation. There were no treatment-related effects in the knee joints, or in the popliteal and inguinal lymph nodes in any animal in this study. It is concluded that although no local toxicity was found by intra-articular ACZ885 injection during a 3-day observation period after dosing in marmosets, there were treatment-related systemic findings suggestive of inflammation and/or infection. The TK sampling confirmed systemic exposure in the treated marmosets, with mean serum concentrations of 99.84 mcg/ml at 24 hours and 86.9 mcg/ml at 48 hours after injection.

2.6.6.2 Single-dose toxicity: no single dose toxicity studies were conducted

2.6.6.3 Repeat-dose toxicity

Study title: ***28-Day Intravenous Administration Toxicity Study with a 2-Month Recovery Period in the Marmoset***

Key study findings:

- No treatment-related effects of IV ACZ885 in standard toxicology evaluation and in assessments of anti-drug antibody, lymphocyte subpopulations and monocytes in marmosets administered up to 100 mg/kg/twice weekly for 4 weeks
- NOAEL = 100 mg/kg/twice weekly IV

Study no.: Novartis Study 0280160, ——Study 1939-003 b(4)
Conducting laboratory and location: ——
Date of study initiation: August 18, 2002
GLP compliance: Yes
QA report: yes (x) no ( )
Drug ACZ885, **lot #** (Batch) 3754, **and % purity:** 98% —— -95% (by SEC) b(4)

Methods

Doses: 0 (vehicle control), 10 (LD), 30 (MD), and 100 (HD) mg/kg; doses selected based on 1X, 3X, and 10X estimated MRHD in clinical trials
Species/strain: Marmoset monkey (*Callithrix jacchus*, [redacted] b(4)
Number/sex/group or time point (main study): 3/sex/dose
Animal allocation (from the original BLA submission):

Group	Number/sex	Animal numbers (Terasys numbers*)		Test item	
		Males	Females	Dose Levels (mg/kg/twice weekly)	Application Volume (mL/kg)
1 control	5 M / 5 F	41206M (101), 41273M (102), 41304M (103), 41306M (104), 41310M (105),	41208F (151), 41210F (152), 41214F (153), 41328F (154), 41329F (155)	0	5
2 low	3 M / 3 F	41198M (201), 41205M (202), 41280M (203)	41209F (251), 41322F (252), 41325F (253)	10	0.5
3 intermediate	3 M / 3 F	41202M (301), 41203M (302), 41305M (303)	41282F (351), 41320F (352), 41323F (353)	30	1.5
4 high	5 M / 5 F	41199M (401), 41200M (402), 41307M (403), 41308M (404), 41309M (405)	41207F (451), 41213F (452), 41281F (453), 41326F (454), 41327F (455)	100	5

* Terasys = in-life life data recording system, the numbers are shown in brackets

Route, formulation, volume, and infusion rate: ACZ885 provided pre-mixed in 20 mg/ml vials (formulation could not be determined from the Certificate of Analysis for test article and placebo) for Intravenous (IV) administration by slow bolus injection at 0, 0.5, 1.5, 5 ml/kg (control, LD, MD, and HD groups, respectively) twice weekly for 4 weeks (total 8 infusions)
Satellite groups: 2/sex/dose (control & HD, evaluation of 8-wk recovery)
Age: 1-3 years
Weight: 279-465 g
Additional study design/methodology: Animals housed individually in stainless steel cages, 24-28 degC room temperature, 30%-70% humidity, 12-hour light/dark cycle; food available twice daily with fruit treat after dosing; tap water provided *ad libitum*

Observations and times:

Mortality: Twice daily
Clinical signs: Twice daily pre- and post-dose, usually beginning and end of work day, with additional observations at 1-4 hours after dosing
Body weights: Baseline (before start of treatment phase) and pre-dose, then once weekly during treatment and recovery phases

Food consumption: Once daily
Ophthalmoscopy: Baseline and Treatment Week 4
EKG: Baseline, Dosing Week 4, and end of 8-week recovery phase, at pre-dose, and 2 hours after treatment
Hematology:

- Blood samples (3.3 ml) from femoral or brachial vein on Day 24 from all animals at pre-dose, in Treatment Week 4 and after 8-week recovery phase
- Standard parameters assessed (hemoglobin, mean corpuscular hemoglobin, mean corpuscular volume, packed cell volume, platelet count, red blood cell count, reticulocytes, total and differential white blood cell count)

Bone Marrow Analysis: Bone marrow smears at necropsy
Clinical chemistry:

- Blood samples (3.3 ml) from femoral or brachial vein on Day 24 from all animals at pre-dose, in Treatment Week 4 and after 8-week recovery phase
- Standard parameters assessed (alanine aminotransferase, albumin, albumin/globulin ratio, alkaline phosphatase, aspartate aminotransferase, blood urea nitrogen, calcium, chloride, creatinine, creatine kinase, gamma glutamyl transferase, globulin, glucose, inorganic phosphorus, potassium, protein electrophoresis, sodium, total bilirubin, total cholesterol, total protein, and triglycerides)

Urinalysis:

- 16-hour samples collected overnight from all animals at pre-dose, Week 4 and after 8-week recovery phase
- Standard parameters assessed (bilirubin, blood, glucose, ketones, microscopy of sediment, pH, protein, reducing substances, specific gravity, urobilinogen, and volume)

Toxicokinetics (TK): Blood samples (0.3 ml) from brachial or saphenous vein at pre-dose, Treatment Day 1 and Week 4, and end of 8-week recovery, at pre-dose and 5 minutes, and 1, 8, and 24 hours after dosing
Gross pathology: All animals after treatment and recovery phases
Organ weights:

- All animals after treatment and recovery phases
- Standard organ list (adrenals, epididymides, heart, kidneys, brain (cerebral cortex, thalamus, midbrain, medulla, cerebellum, liver, ovaries, pituitary, prostate, seminal vesicles, spleen, testes, thyroid, and parathyroids)
- Paired organs weighted separately

Histopathology: Adequate Battery: yes (x), no ( )
Peer review: yes ( ), no (x)

- Standard organ and tissue samples examined (aorta (arch and anterior abdominal), application/injection site, bone marrow smear (femur), brain (cerebral cortex, thalamus, midbrain, medulla, cerebellum), cecum, colon, duodenum, dura mater, epididymides, esophagus, eyes and optic nerves, adrenals, femur with bone marrow and articular surface, gall bladder, gross lesions, heart, ileum, jejunum, kidneys, lacrimal gland, liver, lungs (with mainstem bronchi), mammary glands, mandibular lymph nodes, mesenteric lymph nodes, ovaries, pancreas, parotids,

pituitary, prostate, rectum, salivary glands (lingual), salivary glands (mandibular), sciatic nerve, seminal vesicles, skeletal muscle (femur), skin/animal identification, spinal cord cervical, spinal cord (lumbar and thoracic), spleen, sternum with bone marrow, stomach, testes, thymus, thyroid and parathyroids, tongue, trachea, urinary bladder, uterus, and vagina)

Other:

Anti-ACZ885 antibody analyses:

- Sheep anti-ACZ885 serum positive control, pre-treatment serum negative control; treated and control marmoset serum sampled for anti-ACZ885 antibody formation on Day 85, analytical method used Biosensor, ——— b(4)
- 0.4 ml blood samples at pre-dose and before necropsy in recovery animals

Immunophenotyping of lymphocyte subpopulations and monocytes:

- Blood samples (0.5 ml) from all animals at pre-dose and at necropsy following treatment and recovery
- Immunophenotyping of lymphocytes [CD3 (T lymphocyte), CD4 (Helper T cell), CD8 (Cytotoxic T cell), CD14 (monocyte/macrophage), CD16 (NK cell), CD20 (B lymphocyte), CD56 (NK cell)] by flow cytometry

Results

Mortality: No deaths

Clinical signs: No treatment-related effects during treatment and recovery periods

Body weights: No treatment-related effects during treatment and recovery periods

Food consumption: No treatment-related effects during treatment and recovery periods

Ophthalmoscopy: No treatment-related effects during treatment and recovery periods

EKG: No treatment-related effects on heart rate, blood pressures, and ECG parameters including QT interval, during treatment and recovery periods

Hematology: No treatment-related effects during treatment and recovery periods

Clinical chemistry: No treatment-related effects during treatment and recovery periods

Urinalysis: No treatment-related effects during treatment and recovery periods

Gross pathology: No treatment-related effects during treatment and recovery periods

Organ weights: No treatment-related effects during treatment and recovery periods

Histopathology: No treatment-related effects during treatment and recovery periods
Adequate Battery: yes (x), no ( )
Peer review: yes ( ), no (x)

Toxicokinetics:

- Dose-proportional increase in exposure ($AUC_{0.083-24h}$ and C_{max}) from 10-100 mg/kg on Day 1
- Increased exposure at 4-weeks vs. Day 1, suggesting accumulation
- No gender differences in TK parameters
- $t_{1/2}$ 7.9 days in males (M) and 6.5 days in females (F)
- The following TK parameters were observed (from the original BLA submission):

Table 2-1 Mean toxicokinetic parameters of ACZ885 in serum of marmosets on Week 1, administration on Day 1

	10 mg/kg				30 mg/kg				100 mg/kg			
	Males**	SD	Female***	SD	Males**	SD	Female***	SD	Males****	SD	Female****	SD
t_{max}	0.083	*	1	*	0.083	*	0.083 to 1	*	0.083 to 1	*	0.083 to 1	*
C_{max}	272.28	3.30	167.86	18.12	847.27	70.47	606.70	64.35	2164.66	277.63	2346.51	47.27
C_{max}/dose	27.23	0.33	16.8	1.8	21.58	2.35	20.22	2.15	21.65	2.78	23.47	0.47
AUC(0.083-24h)	3688	319	2942	147	10447	2224	9979	2037	35166	3770	37666	2965
AUC(0.083-24h)/dose	368.8	31.9	294	15	348.2	74.1	332.6	67.9	351.7	37.7	376.7	28.6

Units: t [h], C [µg/mL], C/dose [(µg/mL)/(mg/kg)], AUC [h·µg/mL], AUC/dose [(h·µg/mL)/(mg/kg)].
*: not available or applicable.
**: n=2
***: n=3
****: n=6

Table 2-2 Mean toxicokinetic parameters of ACZ885 in serum of marmosets on Week 4, administration on Day 28

	10 mg/kg				30 mg/kg				100 mg/kg			
	Males**	SD	Female**	SD	Males**	SD	Female**	SD	Males***	SD	Female***	SD
t_{max}	0.083	*	0.083 to 1	*	0.083 to 1	*	0.083	*	0.083 to 8	*	0.083 to 1	*
C_{max}	240.68	113.84	276.01	27.16	862.23	185.14	978.37	130.89	2563.03	743.59	2901.58	351.68
C_{max}/dose	24.1	11.4	27.6	2.7	28.7	6.2	32.5	4.4	29.6	7.4	29.0	3.5
AUC(0.083-24h)	4362	1902	5001	584	15477	3556	14480	1074	54553	11925	52716	4607
AUC(0.083-24h)/dose	439	190	500	58	516	129	483	36	546	119	527	46
									Males from recovery period, n=2	SD	Females from recovery period, n=2	SD
$t_{1/2}$									7.9	0.1	6.5	0.1

Units: t_{max} [h], $t_{1/2}$ [days], C [µg/mL], C/dose [(µg/mL)/(mg/kg)].
AUC(0.083-24h) [h·µg/mL], AUC(0.083-24h)/dose [(h·µg/mL)/(mg/kg)].
*: not available or applicable.
**: n=3
***: n=6

Other:

Anti-ACZ885 antibody analyses:

- No anti-ACZ885 antibodies found, however, ACZ885 levels (1.02-2.90 mcg/ml) found at the HD (recovery) could have neutralized anti-ACZ885 antibodies if present

Immunophenotyping of lymphocyte subpopulations and monocytes:

- No treatment-related findings that were consistent across dose groups, although within-group and within-animal variability was observed with both increases/decreases in specific lymphocyte subpopulations

- Total leucocyte counts were highly variable in the following animals:
  - Increased in the following animals:
    - Group 1 Control (41304M) 19.6 X 1000/mcl at predose
    - Group 1 (41329F) 19.4 X 1000/mcl at 6 weeks vs. 11.1 X 1000/mcl at predose
    - Group 4 (41199M) 17.3 X 1000/mcl at 6 weeks vs. 12.2 X 1000/mcl at predose and vs. control mean of 9.1 X 1000/mcl in control M at 6 weeks

Study title: ***26-Week Intravenous Administration Toxicity Study with a 6-Week Recovery Period in the Marmoset***

Key study findings:

- No treatment-related effects on standard toxicology parameters, male reproductive system (sperm count, motility, morphology, testicular size, circulating hormones, and microscopic examination of testicular tissue), and on lymphocyte subpopulations and monocytes by IV ACZ885 administered twice weekly at doses of 10-100 mg/kg for 26 weeks in adult male and female marmosets
- No anti-ACZ885 antibodies detected
- NOAEL 100 mg/kg/twice weekly IV for 26 weeks

Study no.: Novartis Study 0380070, —— Study 1939-004 b(4)
Conducting laboratory and location
Date of study initiation: June 16, 2003
GLP compliance: Yes
QA report: yes (x) no ( )
Drug ACZ885 in 5 ml vials at 30 mg/ml, 150 mg/vial, **lot #** (Batch) 4535, **and % purity:** b(4)
99.3% ——) – 99.9% (by Size Exclusion Chromatography)

Methods

Doses: 0 (vehicle control), 10 (LD), 30 (MD), and 100 (HD) mg/kg/twice weekly, based on 1X, 3X, and 10X anticipated MRHD, on consistency with doses used in other toxicity studies, and on the results of a 4-week IV tolerability study in marmosets

Species/strain: Marmoset monkey (*Callithrix jacchus*)

Number/sex/group or time point (main study): 4/sex/dose group; the animal allocation is presented in the following table (from the original BLA submission):

Table 3-3 Study design, animal allocation and test item dosages

Group Number	Group Designation	Color Code	Dose Level (mg/kg/ twice weekly)	Animal/Group Males (Main Study /Recovery)	Females (Main Study /Recovery)	Application Volume (mL/kg)
1	Reference/Placebo	White	0	4/2	4/2	3.33
2	Low	Blue	10	4	4	0.33
3	Intermediate	Green	30	4	4	1.0
4	High	Red	100	4/2	4/2	3.33

Note: The animals selected to serve as a recovery have undergone a 6-week treatment-free period following the last administration, to determine the reversibility of possible effects observed.

The following animal numbers were assigned:
Controls: Males 101-106; Females 151-156
LD (10 mg/kg): Males 201-204; Females 251-254
MD (30 mg/kg): Males 301-304; Females 351-354
HD (100 mg/kg): Males 401-406: Females 451-456

Route, formulation, volume, and infusion rate: ACZ885 provided in ready-to-use formulation, administered twice weekly by IV bolus (saphenous vein) at 0.33-3.33 ml/kg for 26 consecutive weeks
Satellite groups used for toxicokinetics or recovery: 2/sex controls and HD animals for the 6-week reversibility group
Age: 1.5-4 years
Weight: 315-455 g
Additional and unique methodology:

- Animals were pair-housed (same sex) in climate-controlled facility at 20-28 degC temperature, 30%-70% humidity, with 12-hours light/dark cycle
- Fresh food provided twice daily with rewards of fruit and mealworm after dosing; water was provided *ad libitum*
- Semen collected using rectal probe stimulation-induced ejaculates for sperm evaluation and testicular size was measured in all males at baseline and in Treatment Weeks 14 and 24, and Recovery Week 5
- Hormones analyzed for testosterone-T-(radio-immuno assay) in blood samples (0.6 ml, brachial vein) from in all males at baseline, during Treatment Weeks 13 and 26, and in Recovery Week 5
- Immunophenotyping of lymphocytes conducted in all animals at baseline, and end of Recovery phase
- Anti-ACZ885 antibody evaluation conducted on all animals at baseline and at end of Recovery phase

Observations and times

Mortality: Twice daily throughout Treatment and recovery phases

Clinical signs: Twice daily throughout Treatment and recovery phases
Body weights: Baseline and once weekly throughout Treatment and recovery phases
Food consumption: Daily (assessed for paired marmosets, estimated for individual animals)

Semen:

- Semen was collected using rectal probe stimulation-induced ejaculates for sperm evaluation
  - Sperm motility:
    - Analyzed using Computer-Assisted Sperm Analysis (CASA) system — (automatically measures motility) in fluid from *Vas deferens* b(4)
    - Analyzed microscopically (debris, other sperm cells seen in CASA evaluation)
  - Sperm number
    - Determined in semen exudate and coagulum using CASA system — expressed as spermatozoa X 10^6/ml b(4)
    - Analyzed microscopically by counting
    - Also analyzed using hematocytometer
  - Sperm morphology
    - Assessed from Papanicolaou-stained exudate smears

Testicular size: measured using caliper (width and length) in all males, twice per time-point at baseline, in Treatment Weeks 14 and 24, and Recovery Week 5
Testicular tissue:

- Analyzed by flow cytometry and DNA staining for testicular cell population quantitation
- The following flow cytometric data (% testicular germ cells and sperm using Flow Cytometry ——— , were reported: b(4)
  - HC (%): percent elongated spermatids
  - 1C (%): percent round and elongated spermatids
  - 2C (%): percent spermatogonia and somatic cells
  - S-ph (%):percent cells synthezising DNA
  - 4C (%): percent spermatocytes and G2-spermatogonia

Ophthalmoscopy: Baseline, Treatment Weeks 13 and 26, and at the end of the 6-week Recovery phase
EKG: Baseline, Treatment Weeks 13 and 26, and at the end of the 6-Week Recovery phase, at time of dosing and 2 hours post-dose during Treatment period, and at same times (without dosing) during baseline and recovery,
Hematology:

- Blood samples (3.3 ml) from the femoral or brachial vein at baseline, during Treatment Weeks 13 and 26, and at the end of the 6-Week Recovery phase
- Standard parameters assessed: erythrocytes, hemoglobin, mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration, reticulocytes, total and differential white blood cell count, white

blood cell differential, platelets, packed cell volume, activated partial thromboplastin time, and prothrombin time

Bone marrow smears: at necropsy

Clinical chemistry:

- Blood samples (3.3 ml) from the femoral or brachial vein at baseline, during Treatment Weeks 13 and 26, and at the end of the 6-Week Recovery phase
- Standard parameters assessed: aspartate aminotransferase, alkaline phosphatase (total), sodium, calcium, chloride, albumin, albumin/globulin ratio, glucose, total bilirubin, creatinine, protein electrophoresis, blood urea nitrogen, alanine aminotransferase, gamma glutamyl transferase, potassium, inorganic phorphorus, total protein, globulin, total cholesterol, triglycerides, and creatine kinase

Male Hormone Analysis: Hormones analyzed for testosterone-T-(radio-immuno assay) in blood samples (0.6 ml, brachial vein) from in all males taken at baseline, during Treatment Weeks 13 and 26, and in Recovery Week 5

Immunophenotyping: Immunophenotyping of lymphocytes by flow cytometry conducted in all animals using blood samples (0.6 ml) taken at baseline, and end of Treatment and Recovery phases, for CD3, CD4, CD8, CD14, CD16, CD20, and CD56

Urinalysis:

- 16-hour urine samples collected at baseline, during Treatment Weeks 13 and 26, and at the end of the 6-Week Recovery phase
- Standard parameters assessed: bilirubin, blood (leucocytes & hemoglobin/erythrocytes), glucose, ketones, microscopy of sediment, pH, protein, reducing substances (nitrite), specific gravity, bilinogen, and volume

Gross pathology: All animals, at necropsy after 26 week Treatment and 6-week recovery

Organ weights:

- All terminal kill animals at necropsy
- The following organs were weighed (separately for paired organs): adrenals, epididymides, heart, kidneys, brain (cerebral cortex, thalamus, midbrain, medulla, cerebellum), seminal vesicles, spleen, testes, thyroid and parathyroids

Histopathology: Adequate Battery: yes (x), no ( )
Peer review: yes ( ), no (x)

- All terminal kill animals at necropsy
- The following organs and tissues were examined: adrenals, aorta (arch and anterior abdominal), application/injection site, bone marrow smear (femur), brain (cerebral cortex, thalamus, midbrain, medulla, cerebellum), cecum, colon, duodenum, dura mater, epididymides, esophagus, eyes and optic nerves, femur with bone marrow and articular surface, gall bladder, gross lesions, heart, ileum, jejunum, kidneys, lacrimal gland, liver, lungs with mainstem bronchi, mammary glands, lymph nodes (mandibular, mesenteric), ovaries, pancreas, parotids, pituitary, prostate, rectum, salivary glands (mandibular), sciatic nerve, seminal vesicles, skeletal muscle (femur), skin, spinal cord (cervical, lumbar, thoracic), spleen sternum with bone marrow, stomach, testes, thymus, thyroid and parathyroids, tongue, trachea, urinary bladder, uterus, vagina, and blood samples for flow cytometry and anti-ACZ885 antibodies

Toxicokinetics: Blood samples (0.3 ml) from the brachial or saphenous vein from all animals on Treatment Day 1, Weeks 11 and 23 (at 5 minutes and 1, 8, and 24 hours after dosing), and at the end of the 6-Week Recovery phase

Anti-ACZ885 antibody evaluation: Blood samples (0.4 ml) from all animals at baseline and at end of Recovery phase, analyzed using Biosensor —, not conducted under GLP. b(4)

Results

Mortality: No treatment-related deaths; one Control female was terminated on Day 117 with hematoma at upper leg related to blood withdrawal on Study Day 86. The hematoma had burst and the marmoset went into shock from blood loss.

Clinical signs: No treatment-related effects during the Treatment and Recovery phases

Body weights: No treatment-related effects during the Treatment and Recovery phases

Food consumption: No treatment-related effects during the Treatment and Recovery phases

Sperm and testicular size evaluation:

- No treatment-related effects on sperm morphology, motility and number during the Treatment and Recovery phases
- Reduced sperm count observed in all groups including controls
- No treatment-related effects on testicular size at the end of the Treatment and Recovery phases
- The results of the sperm and testicular size evaluation (group means) provided by the Applicant are presented in the following tables:

Group Mean Ejaculate Data CLE Study No.1939-004

Sperm Count using Microscope (10^6/mL)

Occasion		Group 1 3 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Pre-dose -2	Mean	23.042	15.177	17.237	57.075
	SD	17.264	23.708	19.011	58.014
	SE	7.648	13.638	9.505	23.584
	N	6	3	4	6
Pre-dose -1	Mean	9.951	2.658	39.311	17.314
	SD	11.943	2.627	25.246	24.488
	SE	5.341	1.517	12.623	10.951
	N	5	3	4	5
Week 14	Mean	2.275	13.778	57.313	5.548
	SD	5.017	14.183	58.015	6.336
	SE	2.244	8.188	29.007	2.834
	N	5	3	4	5
Week 24	Mean	12.528	0.000	15.906	12.797
	SD	17.603	0.000	31.729	19.175
	SE	7.186	0.000	15.865	8.575
	N	6	3	4	5
Week 31	Mean	7.039			75.753
	SD	-			-
	SE	-			-
	N	2			2

Standard deviation and standard error not calculated for less than three values

Statistical analysis was performed using SAS release 6.12

Group Mean Ejaculate Data CL# Study No.1939-004

Sperm Count using CASA (10^6/mL)

Occasion		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Pre-dose -2	Mean	36.238	22.833	66.713	67.033
	SD	22.722	33.562	112.205	63.389
	SE	9.276	19.377	56.102	26.083
	N	6	3	4	5
Pre-dose -1	Mean	10.793	3.183	51.688	22.225
	SD	11.394	2.663	33.960	35.763
	SE	5.095	1.537	16.980	15.994
	N	5	3	4	5
Week 14	Mean	2.735	10.700	36.492	4.730
	SD	2.933	13.522	41.600	4.021
	SE	1.312	7.807	24.018	1.798
	N	5	3	3	5
Week 24	Mean	10.525	1.117	11.819	19.420
	SD	13.667	1.073	19.738	28.920
	SE	5.396	0.619	9.869	12.934
	N	6	3	4	5
Week 31	Mean	5.375			766.350
	SD	-			-
	SE	-			-
	N	2			2

Standard deviation and standard error not calculated for less than three values

Statistical analysis was performed using SAS release 6.12

Group Mean Ejaculate Data CLE Study No.1939-004

Sperm Motility using Microscope (%)

Occasion		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Pre-dose -2	Mean	68.1	69.8	62.0	64.0
	SD	8.4	-	8.3	12.4
	SE	3.4	-	4.2	5.0
	N	6	2	4	6
Pre-dose -1	Mean	73.3	67.0	60.4	69.5
	SD	12.8	-	9.8	11.5
	SE	6.4	-	4.9	5.1
	N	4	2	4	5
Week 14	Mean	15.0	49.5	44.7	53.9
	SD	33.5	42.9	32.9	36.2
	SE	15.0	24.8	16.5	18.1
	N	5	3	4	4
Week 24	Mean	27.3	0.0	18.5	37.1
	SD	30.2	-	32.0	34.2
	SE	12.3	-	18.5	15.3
	N	6	2	3	5
Week 31	Mean	61.5			32.5
	SD	-			-
	SE	-			-
	N	1			1

Standard deviation and standard error not calculated for less than three values

Statistical analysis was performed using SAS release 6.12

Group Mean Ejaculate Data CLE Study No.1939-C04

Sperm Motility using CASA (%)

Occasion		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Pre-dose -2	Mean	31.1	11.8	15.1	35.5
	SD	16.4	13.8	10.3	12.7
	SE	6.7	8.0	5.2	5.2
	N	6	3	4	5
Pre-dose -1	Mean	25.7	16.2	26.5	36.5
	SD	32.7	15.0	17.0	25.9
	SE	14.6	8.6	8.5	11.5
	N	5	3	4	5
Week 14	Mean	5.0	18.2	35.8	17.7
	SD	10.4	18.8	31.8	18.0
	SE	4.6	10.8	15.9	8.0
	N	5	3	4	5
Week 24	Mean	25.8	1.3	12.8	36.1
	SD	38.5	1.5	25.5	35.9
	SE	15.7	0.9	12.8	16.0
	N	6	3	4	5
Week 31	Mean	28.3			3.8
	SD	-			-
	SE	-			-
	N	2			2

Standard deviation and standard error not calculated for less than three values

Statistical analysis was performed using SAS release 6.12

Group Mean Sperm Morphology Data (%) CLE Study No. 1939-004

Occasion Week 24

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
normal	Mean	75.8	-	57.0	88.2
	SD	13.7	-	-	3.7
	SE	7.9	-	-	2.1
	N	3	-	1	3
head defect	Mean	0.8	-	11.0	0.3
	SD	0.5	-	-	0.6
	SE	0.3	-	-	0.3
	N	3	-	1	3
mid piece defect	Mean	19.4	-	21.0	8.3 *
	SD	12.4	-	-	0.8
	SE	7.2	-	-	0.4
	N	3	-	1	3
tail defect	Mean	11.7	-	12.0	4.7
	SD	9.0	-	-	3.9
	SE	5.2	-	-	2.2
	N	3	-	1	3
defects total	Mean	31.6	-	44.0	13.3
	SD	21.4	-	-	5.1
	SE	12.4	-	-	3.0
	N	3	-	1	3
with more than one defect	Mean	7.4	-	8.7	1.5
	SD	7.8	-	-	1.5
	SE	4.5	-	-	0.9
	N	3	-	1	3

Standard deviation and standard error not calculated for less than three values

Statistical analysis was performed using SAS release 6.12
Significantly different from control: * - 95% confidence level

Group Mean Testicular Volumes (mL) CLE Study No.1939-004

a) Testes

Occasion		Group 1 5 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Pre-dose -2	Mean	0.55	0.40	0.36	0.59
	SD	0.14	0.09	0.04	0.11
	SE	0.06	0.05	0.02	0.05
	N	5	4	4	5
Pre-dose -1	Mean	0.57	0.43	0.53	0.66
	SD	0.12	0.07	0.10	0.12
	SE	0.05	0.03	0.05	0.05
	N	5	4	4	5
Week 14	Mean	0.66	0.62	0.57	0.71
	SD	0.15	0.13	0.19	0.16
	SE	0.06	0.07	0.10	0.06
	N	5	4	4	5
Week 24	Mean	0.57	0.53	0.53	0.53
	SD	0.11	0.10	0.10	0.17
	SE	0.05	0.05	0.05	0.07
	N	5	4	4	5
Week 31	Mean	0.54			0.39
	SD	-			-
	SE	-			-
	N	2			2

Standard deviation and standard error not calculated for less than three values

Statistical analysis was performed using SAS release 6.12

Ophthalmoscopy: No treatment-related effects during the Treatment and Recovery phases

EKG: No treatment-related effects on heart rate or cardiac rhythm, including corrected and uncorrected QT interval were observed

Hematology: No treatment-related effects during the Treatment and Recovery phases; the results (group means) of the hematology assessments at the end of treatment provided by the Applicant are presented below:

Group Mean Hematology Data — CLE Study No.1939-004

Occasion Week 26

a) Male Animals

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Reticulocytes (‰)	Mean	46.3	53.1	35.6	71.0
	SD	12.5	24.4	6.0	26.3
	SE	5.1	12.2	3.0	11.8
	N	6	4	4	5
RBC (10 E12/L)	Mean	7.15	6.92	7.65	6.45 *
	SD	0.25	0.43	0.52	0.55
	SE	0.10	0.22	0.26	0.22
	N	6	4	4	5
Hb (mmol/L)	Mean	10.4	10.0	10.7	9.2 *
	SD	0.6	0.3	0.9	0.8
	SE	0.2	0.1	0.5	0.3
	N	6	4	4	5
PCV (%)	Mean	53.3	51.8	54.7	47.9
	SD	2.5	1.2	4.4	4.0
	SE	1.0	0.6	2.2	1.8
	N	6	4	4	5
MCV (fL)	Mean	74.6	75.1	71.5	74.3
	SD	1.8	4.6	2.2	2.3
	SE	0.7	2.3	1.1	0.9
	N	6	4	4	5
MCH (fmol)	Mean	1.454	1.452	1.399	1.424
	SD	0.034	0.075	0.074	0.055
	SE	0.014	0.037	0.037	0.023
	N	6	4	4	5
MCHC (mmol/L)	Mean	19.5	19.4	19.6	19.2
	SD	0.3	0.2	0.5	0.3
	SE	0.1	0.1	0.3	0.1
	N	6	4	4	5

Statistical analysis was performed using SAS release 6.12
Significantly different from control: * - 95% confidence level

Group Mean Hematology Data CLE Study No.1939-004

Occasion Week 26

a) Male Animals (cont.)

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
PT (s)	Mean	5.8	5.7	5.8	5.5
	SD	0.2	0.4	0.2	0.1
	SE	0.1	0.2	0.1	0.0
	N	5	4	4	5
APTT (s)	Mean	21.8	22.4	21.9	23.0
	SD	0.8	1.5	1.9	1.7
	SE	0.3	0.8	0.9	0.7
	N	5	4	4	5
Platelets (10 E9/L)	Mean	553	563	533	519
	SD	62	132	81	203
	SE	25	66	40	83
	N	5	4	4	5
WBC (10 E9/L)	Mean	5.1	5.1	6.0	6.5
	SD	1.5	1.1	1.5	1.5
	SE	0.6	0.5	0.8	0.6
	N	5	4	4	5
Differential WBC - NJ (%)	Mean	0	0	0	0
	SD	0	0	0	0
	SE	0	0	0	0
	N	5	4	4	5
Differential WBC - NSc (%)	Mean	1	2	2	2
	SD	1	1	1	1
	SE	0	0	0	1
	N	5	4	4	5
Differential WBC - NSc (%)	Mean	52	46	59	44
	SD	18	21	10	15
	SE	7	10	5	6
	N	5	4	4	5

Statistical analysis was performed using SAS release 6.12

Group Mean Hematology Data — CLE Study No.1939-004

Occasion Week 26

a) Male Animals (cont.)

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Differential WBC - Ba (%)	Mean	0	1	0	1
	SD	0	1	0	1
	SE	0	0	0	0
	N	5	4	4	5
Differential WBC - E (%)	Mean	5	3	3	3
	SD	3	2	1	2
	SE	1	1	0	1
	N	5	4	4	5
Differential WBC - L (%)	Mean	41	48	37	30
	SD	15	22	9	15
	SE	6	11	5	7
	N	5	4	4	5
Differential WBC - M (%)	Mean	1	0	1	1
	SD	1	1	1	1
	SE	0	0	0	0
	N	5	4	4	5
Differential WBC - Bl (%)	Mean	0	0	0	0
	SD	0	0	0	0
	SE	0	0	0	0
	N	5	4	4	5
Differential WBC - Dc-N[1]	Mean	0	0	0	2 *
	SD	0	0	1	2
	SE	0	0	0	1
	N	5	4	4	5

Dc-N[1] : diverse cells - normoblasts, counted singly, not calculated as a percentage

Statistical analysis was performed using SAS release 6.12
Significantly different from control: * - 95% confidence level

Group Mean Hematology Data CLE Study No.1939-004

Occasion Week 26

b) Female Animals

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Reticulocytes (‰)	Mean	50.2	105.7	47.1	40.1
	SD	10.5	57.5	5.9	7.5
	SE	4.7	43.7	3.0	3.1
	N	5	4	4	5
RBC (10 E12/L)	Mean	6.73	6.41	5.96	6.52
	SD	0.47	0.37	0.55	0.39
	SE	0.21	0.44	0.28	0.16
	N	5	4	4	5
Hb (mmol/L)	Mean	9.8	9.5	9.9	9.3
	SD	0.7	1.1	0.4	0.5
	SE	0.3	0.5	0.2	0.2
	N	5	4	4	5
PCV (%)	Mean	50.2	48.8	52.0	47.9
	SD	2.7	5.4	2.8	2.8
	SE	1.2	2.7	1.4	1.1
	N	5	4	4	5
MCV (fL)	Mean	74.7	76.4	74.9	73.5
	SD	1.5	2.3	2.1	3.5
	SE	0.7	1.2	1.1	1.5
	N	5	4	4	5
MCH (fmol)	Mean	1.463	1.483	1.426	1.421
	SD	0.022	0.042	0.056	0.081
	SE	0.010	0.021	0.033	0.033
	N	5	4	4	5
MCHC (mmol/L)	Mean	19.6	19.4	19.0	19.3
	SD	0.4	0.1	0.4	0.3
	SE	0.2	0.0	0.2	0.1
	N	5	4	4	5

Statistical analysis was performed using SAS release 6.12

Group Mean Hematology Data CLE Study No.1939-004

Occasion Week 26

b) Female Animals (cont.)

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
PT (s)	Mean	5.8	5.8	5.7	5.6
	SD	0.2	0.1	0.1	0.4
	SE	0.1	0.0	0.1	0.2
	N	3	4	4	5
APTT (s)	Mean	23.7	23.4	22.3	23.3
	SD	1.1	1.7	1.5	1.4
	SE	0.5	0.9	0.7	0.6
	N	3	4	4	5
Platelets (10 E9/L)	Mean	516	605	570	589
	SD	119	92	75	157
	SE	53	46	37	64
	N	3	4	4	5
WBC (10 E9/L)	Mean	5.6	5.1	5.2	4.2
	SD	1.3	1.7	0.9	0.8
	SE	0.6	0.9	0.4	0.3
	N	3	4	4	5
Differential WBC - NU (%)	Mean	0	0	0	0
	SD	0	0	0	0
	SE	0	0	0	0
	N	3	4	4	5
Differential WBC - NSc (%)	Mean	1	2	2	2
	SD	1	1	1	1
	SE	0	0	0	0
	N	3	4	4	5
Differential WBC - NSc (%)	Mean	37	46	32	45
	SD	15	3	12	15
	SE	7	1	6	7
	N	3	4	4	5

Statistical analysis was performed using SAS release 6.12

Group Mean Hematology Data — CLE Study No.1939-004

Occasion Week 26

b) Female Animals (cont.)

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Differential WBC - Ba (%)	Mean	0	1	1	0
	SD	1	1	1	1
	SE	0	0	0	0
	N	5	4	4	5
Differential WBC - E (%)	Mean	3	4	1 *	3
	SD	2	2	1	1
	SE	1	1	1	1
	N	5	4	4	5
Differential WBC - L (%)	Mean	56	47	44	50
	SD	16	3	13	15
	SE	7	2	6	6
	N	5	4	4	5
Differential WBC - M (%)	Mean	0	1	0	0
	SD	1	1	1	1
	SE	0	0	0	0
	N	5	4	4	5
Differential WBC - Bl (%)	Mean	0	0	0	0
	SD	0	0	0	0
	SE	0	0	0	0
	N	5	4	4	5
Differential WBC - Oc-N[1]	Mean	2	1	1	1
	SD	1	1	1	1
	SE	0	1	1	0
	N	5	4	4	5

Oc-N[1] : diverse cells - normoblasts, counted singly, not calculated as a percentage

Statistical analysis was performed using SAS release 6.12
Significantly different from control: * - 95% confidence level

Immunophenotyping: No treatment-related effects on lymphocyte subpopulations and monocytes during the Treatment and Recovery phases; the following results, showing group means, were provided by the Applicant:

Leucocyte Count x 1000/µl

male

		Group1	Group 2	Group 3	Group 4
pre-dose	**mean**	**8,4**	**10,1**	**8,3**	**8,5**
	SD	1,6	2,5	3	2,5
	n	6	4	4	6
week 26/27	**mean**	**7,3**	**7,6**	**7**	**8,7**
	SD	1,3	1,9	0,6	3,6
	n	3	4	4	4
recovery week 32	**mean**	**7**			**8**
	SD	-			-
	n	2			2

female

		Group 1	Group 2	Group 3	Group 4
pre-dose	**mean**	**8,3**	**8,1**	**11,1**	**9,5**
	SD	2,5	2	4,9	3,3
	n	6	4	4	6
week 26/27	**mean**	**7**	**7,3**	**9,5**	**6,6**
	SD	2,4	1,1	2,3	2,1
	n	3	4	4	3
recovery week 32	**mean**	**8,05**			**8,1**
	SD	-			-
	n	2			2

Lymphocytes (%)

male

		Group1	Group 2	Group 3	Group 4
pre-dose	**mean**	**52**	**43**	**43**	**56**
	SD	7	13	16	9
	n	6	4	4	6
week 26/27	**mean**	**64**	**61**	**42**	**56**
	SD	14	13	14	15
	n	3	4	4	4
recovery week 32	**mean**	**42**			**63**
	SD	-			-
	n	2			2

female

		Group 1	Group 2	Group 3	Group 4
pre-dose	**mean**	**63**	**47**	**55**	**53**
	SD	9	7	5	8
	n	6	4	4	6
week 26/27	**mean**	**59**	**51**	**42**	**57**
	SD	19	14	8	26
	n	3	4	4	3
recovery week 32	**mean**	**31**			**41**
	SD	-			-
	n	2			2

Monocytes (CD14 bright +) (%)

male

		Group1	Group 2	Group 3	Group 4
pre-dose	mean	4,1	3,6	4	3,6
	SD	1,8	1	1,7	1,1
	n	6	4	4	6
week 26/27	mean	5,4	4	3,6	3,7
	SD	0,6	0,3	1,6	1,7
	n	3	4	4	4
recovery week 32	mean	3,7			7,9
	SD	-			-
	n	2			2

female

		Group 1	Group 2	Group 3	Group 4
pre-dose	mean	4,5	5,2	4,6	5,6
	SD	1,5	2,1	1,3	2,1
	n	6	4	4	6
week 26/27	mean	5,6	5,2	5,3	4,3
	SD	3,5	1,7	1,9	1,6
	n	3	4	4	4
recovery week 32	mean	10,5			4,8
	SD	-			-
	n	2			2

B-Lymphocytes (counts/µl)

male

		Group1	Group 2	Group 3	Group 4
pre-dose	mean	870	1048	825	1108
	SD	321	395	291	463
	n	6	4	4	6
week 26/27	mean	1183	1216	663	1070
	SD	286	859	257	449
	n	3	4	4	4
recovery week 32	mean	576			852
	SD	-			-
	n	2			2

female

		Group 1	Group 2	Group 3	Group 4
pre-dose	mean	1303	810	1488	1210
	SD	536	279	663	668
	n	6	4	4	6
week 26/27	mean	935	735	943	1053
	SD	750	123	84	931
	n	3	4	4	3
recovery week 32	mean	707			644
	SD	-			-
	n	2			2

B-Lymphocytes (%)

male

		Group1	Group 2	Group 3	Group 4
pre-dose	**mean**	**20**	**25**	**25**	**23**
	SD	4	6	2	5
	n	6	4	4	6
week 26/27	**mean**	**24**	**23**	**22**	**23**
	SD	5	11	3	6
	n	4	4	4	4
recovery week 32	**mean**	**19**			**18**
	SD	-			-
	n	2			2

female

		Group 1	Group 2	Group 3	Group 4
pre-dose	**mean**	**25**	**21**	**24**	**23**
	SD	5	4	3	4
	n	6	4	4	6
week 26/27	**mean**	**20**	**21**	**25**	**25**
	SD	5	6	5	8
	n	3	4	4	4
recovery week 32	**mean**	**29**			**19**
	SD	-			-
	n	2			2

Pan-T-Lymphocytes (counts/µl)

male

		Group1	Group 2	Group 3	Group 4
pre-dose	**mean**	**2963**	**2770**	**1965**	**3282**
	SD	511	415	421	1016
	n	6	4	4	6
week 26/27	**mean**	**2938**	**3110**	**2083**	**3408**
	SD	205	906	570	1388
	n	4	4	4	4
recovery week 32	**mean**	**2137**			**3260**
	SD	-			-
	n	2			2

female

		Group 1	Group 2	Group 3	Group 4
pre-dose	**mean**	**3142**	**2705**	**4210**	**3438**
	SD	431	446	2280	1288
	n	6	4	4	6
week 26/27	**mean**	**2824**	**2584**	**2498**	**2365**
	SD	1854	913	439	995
	n	3	4	4	3
recovery week 32	**mean**	**1529**			**2323**
	SD	-			-
	n	2			2

Pan-T-Lymphocytes (%)

male

		Group1	Group 2	Group 3	Group 4
predose	mean	69	68	62	70
	SD	4	5	7	4
	n	6	4	4	6
6 months	mean	66	68	72	71
	SD	6	8	2	5
	n	4	4	4	4
recovery	mean	70			68
	SD	-			-
	n	2			2

female

		Group 1	Group 2	Group 3	Group 4
predose	mean	64	72	68	69
	SD	6	3	5	4
	n	6	4	4	6
6 months	mean	64	68	65	68
	SD	4	6	6	9
	n	3	4	4	4
recovery	mean	63			72
	SD	-			-
	n	2			2

T-Helper-Lymphocytes (counts/µl)

male

		Group1	Group 2	Group 3	Group 4
pre-dose	mean	1875	1900	1315	2190
	SD	237	296	296	759
	n	6	4	4	6
week 26/27	mean	1991	2161	1535	2365
	SD	156	576	391	1066
	n	3	4	4	4
recovery week 32	mean	1268			1788
	SD	-			-
	n	2			2

female

		Group 1	Group 2	Group 3	Group 4
pre-dose	mean	1933	1678	2553	1793
	SD	367	187	1320	727
	n	6	4	4	6
week 26/27	mean	1826	1707	1700	1367
	SD	1241	716	274	543
	n	3	4	4	3
recovery week 32	mean	1050			1183
	SD	-			-
	n	2			2

T-Helper-Lymphocytes (%)

male

		Group1	Group 2	Group 3	Group 4
pre-dose	**mean**	**44**	**47**	**42**	**46**
	SD	5	6	8	4
	n	6	4	4	6
week 26/27	**mean**	**44**	**48**	**53**	**48**
	SD	1	8	3	6
	n	4	4	4	4
recovery week 32	**mean**	**42**			**38**
	SD	-			-
	n	2			2

female

		Group 1	Group 2	Group 3	Group 4
pre-dose	**mean**	**39**	**45**	**42**	**36**
	SD	5	5	5	5
	n	6	4	4	6
week 26/27	**mean**	**41**	**45**	**44**	**40**
	SD	2	7	4	5
	n	3	4	4	4
recovery week 32	**mean**	**43**			**38**
	SD	-			-
	n	2			2

T-Suppressor/cytotoxic Lymphocytes (counts/µl)

male

		Group1	Group 2	Group 3	Group 4
pre-dose	**mean**	**1122**	**820**	**598**	**1050**
	SD	401	79	176	290
	n	6	4	4	6
week 26/27	**mean**	**797**	**874**	**531**	**975**
	SD	82	267	166	315
	n	4	4	4	4
recovery week 32	**mean**	**818**			**1551**
	SD	-			-
	n	2			2

female

		Group 1	Group 2	Group 3	Group 4
pre-dose	**mean**	**1138**	**1068**	**1425**	**1530**
	SD	194	240	639	482
	n	6	4	4	6
week 26/27	**mean**	**920**	**823**	**828**	**932**
	SD	554	294	137	304
	n	3	4	4	3
recovery week 32	**mean**	**466**			**1139**
	SD	-			-
	n	2			2

T-Suppressor/cytotoxic Lymphocytes (%)

male

		Group1	Group 2	Group 3	Group 4
pre-dose	mean	26	20	19	23
	SD	5	3	3	4
	n	6	4	4	6
week 26/27	mean	20	19	19	21
	SD	5	2	4	4
	n	4	4	4	4
recovery week 32	mean	26			32
	SD	-			-
	n	2			2

female

		Group 1	Group 2	Group 3	Group 4
pre-dose	mean	23	28	24	32
	SD	5	2	2	6
	n	6	4	4	6
week 26/27	mean	21	22	22	28
	SD	2	5	1	9
	n	3	4	4	4
recovery week 32	mean	19			34
	SD	-			-
	n	2			2

CD4/CD8-Ratio

male

		Group1	Group 2	Group 3	Group 4
pre-dose	mean	1,7	2,3	2,2	2
	SD	0,5	0,2	0,7	0,4
	n	6	4	4	6
week 26/27	mean	2,3	2,5	3	2,4
	SD	0,5	0,3	0,6	0,5
	n	4	4	4	4
recovery week 32	mean	1,8			1,3
	SD	-			-
	n	2			2

female

		Group 1	Group 2	Group 3	Group 4
pre-dose	mean	1,8	1,6	1,8	1,2
	SD	0,4	0,2	0,1	0,3
	n	6	4	4	6
week 26/27	mean	1,9	2,1	2,1	1,5
	SD	0,2	0,5	0,3	0,3
	n	3	4	4	3
recovery week 32	mean	2,3			1,2
	SD	-			-
	n	2			2

NK-Cells (counts/µl)

male

		Group1	Group 2	Group 3	Group 4
pre-dose	mean	345	345	423	358
	SD	55	68	304	106
	n	6	4	4	6
week 26/27	mean	229	243	177	250
	SD	32	49	97	84
	n	4	4	4	4
recovery week 32	mean	234			615
	SD	-			-
	n	2			2

female

		Group 1	Group 2	Group 3	Group 4
pre-dose	mean	457	335	660	468
	SD	147	93	476	225
	n	6	4	4	6
week 26/27	mean	316	230	380	137
	SD	133	19	103	45
	n	3	4	4	3
recovery week 32	mean	189			359
	SD	-			-
	n	2			2

NK-cells (%)

male

		Group1	Group 2	Group 3	Group 4
predose	mean	8	9	12	8
	SD	1	3	6	1
	n	6	4	4	6
6 months	mean	5	6	6	6
	SD	1	2	2	1
	n	4	4	4	4
recovery	mean	8			12
	SD	-			-
	n	2			2

female

		Group 1	Group 2	Group 3	Group 4
predose	mean	9	9	11	9
	SD	3	2	7	3
	n	6	4	4	6
6 months	mean	8	7	10	4
	SD	4	3	4	1
	n	3	4	4	3
recovery	mean	8			10
	SD	-			-
	n	2			2

K = Kill, R = Recovery, cb = clotted blood

Clinical chemistry: No treatment-related effects during the Treatment and Recovery phases; the results of the clinical chemistry assessments at the end of the treatment period (group means) provided by the Applicant, are presented below:

Group Mean Clinical Chemistry Data — CLE Study No.1939-004

Occasion Week 26

a) Male Animals

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Total Bilirubin (µmol/L)	Mean	3.15	2.30	2.97	3.38
	SD	0.80	2.16	0.50	0.83
	SE	0.33	1.08	0.25	0.34
	N	6	4	4	5
Creatinine (µmol/L)	Mean	44.03	41.36	45.22	50.15
	SD	6.63	4.18	5.25	4.29
	SE	2.71	2.09	2.62	1.75
	N	6	4	4	5
BUN (mmol/L)	Mean	2.91	3.72	2.99	2.93
	SD	0.43	1.79	0.17	0.37
	SE	0.18	0.90	0.08	0.15
	N	6	4	4	5
AST (U/L)	Mean	105.03	113.80	114.13	130.94
	SD	28.89	32.78	21.57	53.73
	SE	11.80	16.39	10.84	21.94
	N	6	4	4	5
ALT (U/L)	Mean	0.80	2.40	4.09	18.62
	SD	-	-	-	-
	SE	-	-	-	-
	N	1	2	1	2
Total AP (U/L)	Mean	153.17	174.54	153.07	139.23
	SD	35.56	63.89	51.88	16.37
	SE	14.52	31.94	25.94	6.63
	N	5	4	4	5
GGT (U/L)	Mean	15.64	27.35	15.83	16.20
	SD	9.78	28.15	5.14	20.45
	SE	3.99	14.07	2.57	8.35
	N	6	4	4	5

Standard deviation and standard error not calculated for less than three values

Statistical analysis was performed using SAS release 6.12

Group Mean Clinical Chemistry Data — CLE Study No.1939-024

Occasion Week 26

a) Male Animals (cont.)

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Glucose (mmol/L)	Mean	5.89	5.40	5.28	5.72
	SD	0.78	2.30	1.38	1.44
	SE	0.32	1.45	0.69	0.59
	N	6	4	4	5
Inorganic Phosphorus (mmol/L)	Mean	1.35	1.18	1.00	1.21
	SD	0.18	0.17	0.19	0.08
	SE	0.07	0.08	0.09	0.03
	N	6	4	4	5
Calcium (mmol/L)	Mean	2.91	3.01	2.90	2.83
	SD	0.07	0.10	0.06	0.16
	SE	0.03	0.05	0.03	0.05
	N	6	4	4	5
Sodium (mmol/L)	Mean	158.39	159.94	157.38	159.91
	SD	1.72	1.44	2.04	2.58
	SE	0.70	0.72	1.02	1.05
	N	6	4	4	5
Potassium (mmol/L)	Mean	4.53	4.54	4.13	4.19
	SD	0.22	0.61	0.61	0.23
	SE	0.09	0.31	0.31	0.12
	N	6	4	4	5
Chloride (mmol/L)	Mean	110.35	109.94	109.05	108.33 *
	SD	1.14	1.07	1.05	1.02
	SE	0.47	0.54	0.53	0.42
	N	6	4	4	5
Total Cholesterol (mmol/L)	Mean	5.28	4.31	5.18	5.54
	SD	0.51	0.42	0.43	1.33
	SE	0.21	0.21	0.21	0.56
	N	6	4	4	5

Statistical analysis was performed using SAS release 6.12
Significantly different from control: * - 95% confidence level

Group Mean Clinical Chemistry Data CLE Study No.1939-004

Occasion Week 26

a) Male Animals (cont.)

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Triglycerides (mmol/L)	Mean	1.08	1.67	0.90	1.23
	SD	0.18	1.64	0.19	0.55
	SE	0.08	0.82	0.10	0.23
	N	5	4	4	5
Total Protein (g/L)	Mean	82.43	85.01	86.86	88.46
	SD	2.85	5.16	5.33	4.67
	SE	1.16	2.58	2.67	1.91
	N	5	4	4	5
Creatine Kinase (U/L)	Mean	158.85	203.59	124.06	545.75 *
	SD	56.24	113.91	15.36	431.23
	SE	27.04	56.96	8.18	176.07
	N	5	4	4	5
Albumin (g/L)	Mean	54.67	58.19	54.99	53.41
	SD	1.55	4.82	4.84	6.27
	SE	0.63	2.41	2.42	2.56
	N	5	4	4	5
Globulin (g/L)	Mean	27.77	26.82	31.87	35.05 *
	SD	2.58	3.50	1.61	4.94
	SE	1.05	1.80	0.81	2.02
	N	5	4	4	5
A/G Ratio	Mean	1.99	2.21	1.73	1.55 *
	SD	0.21	0.41	0.16	0.36
	SE	0.09	0.21	0.08	0.15
	N	5	4	4	5

Statistical analysis was performed using SAS release 6.12
Significantly different from control: * - 95% confidence level

Group Mean Clinical Chemistry Data CLE Study No.1939-004

Occasion Week 26

a) Male Animals (cont.)

Protein Electrophoresis Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Albumin (%)	Mean	66.9	68.4	63.9	60.1 *
	SD	2.2	3.4	2.6	6.0
	SE	0.9	1.7	1.3	2.4
	N	6	4	4	6
Alpha1-Globulin (%)	Mean	2.6	2.4	2.5	3.2
	SD	0.3	0.6	0.2	0.6
	SE	0.1	0.3	0.1	0.2
	N	6	4	4	6
Alpha2-Globulin (%)	Mean	9.6	9.1	10.0	9.3
	SD	1.0	1.2	0.8	2.1
	SE	0.4	0.6	0.4	0.9
	N	6	4	4	6
Beta Globulin (%)	Mean	10.1	9.3	8.9	10.5
	SD	0.3	0.9	1.4	1.3
	SE	0.1	0.4	0.7	0.5
	N	6	4	4	6
Gamma Globulin (%)	Mean	10.9	10.7	14.8 *	16.4 *
	SD	1.5	3.1	0.8	3.3
	SE	0.5	1.5	0.4	1.5
	N	6	4	4	6
A/G Ratio	Mean	2.03	2.19	1.79	1.55 *
	SD	0.20	0.37	0.22	0.37
	SE	0.08	0.18	0.11	0.15
	N	6	4	4	6

Statistical analysis was performed using SAS release 6.12
Significantly different from control: * - 95% confidence level

Group Mean Clinical Chemistry Data CLE Study No.1939-004

Occasion Week 26

D) Female Animals

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Total Bilirubin (µmol/L)	Mean	3.25	3.73	3.42	3.51
	SD	0.83	0.99	0.76	0.88
	SE	0.37	0.50	0.38	0.35
	N	5	4	4	5
Creatinine (µmol/L)	Mean	51.29	42.93	50.65	43.60
	SD	6.78	4.94	2.09	3.53
	SE	3.03	2.47	1.04	1.44
	N	5	4	4	5
BUN (mmol/L)	Mean	2.55	2.97	3.39	3.43
	SD	0.69	0.57	0.56	0.77
	SE	0.31	0.28	0.28	0.31
	N	5	4	4	5
AST (U/L)	Mean	128.57	93.72	103.09	117.01
	SD	20.64	15.40	22.30	35.93
	SE	9.23	7.70	11.15	15.08
	N	5	4	4	5
ALT (U/L)	Mean	5.85	2.72	2.51	3.14
	SD	7.78	-	-	4.07
	SE	3.89	-	-	2.35
	N	4	2	1	3
Total AP (U/L)	Mean	104.83	104.36	123.31	125.38
	SD	34.95	7.35	52.10	56.73
	SE	15.63	3.68	26.05	23.15
	N	5	4	4	5
GGT (U/L)	Mean	39.22	8.09	9.09	9.87
	SD	49.67	4.08	7.04	7.82
	SE	22.21	2.04	3.52	3.19
	N	5	4	4	5

Standard deviation and standard error not calculated for less than three values

Statistical analysis was performed using SAS release 6.12

Group Mean Clinical Chemistry Data CLE Study No.1939-004

Occasion Week 26

b) Female Animals (cont.)

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Glucose (mmol/L)	Mean	7.13	5.93	6.05	4.48
	SD	2.33	0.59	1.79	0.91
	SE	1.04	0.30	0.90	0.37
	N	5	4	4	5
Inorganic Phosphorus (mmol/L)	Mean	1.39	1.19	1.56	1.09 *
	SD	0.29	0.08	0.52	0.24
	SE	0.13	0.04	0.26	0.10
	N	5	4	4	5
Calcium (mmol/L)	Mean	2.93	2.91	2.91	2.90
	SD	0.15	0.03	0.14	0.20
	SE	0.07	0.01	0.07	0.09
	N	5	4	4	5
Sodium (mmol/L)	Mean	162.58	161.00	163.78	163.33
	SD	2.99	1.24	1.89	4.29
	SE	1.34	0.62	0.94	1.75
	N	5	4	4	5
Potassium (mmol/L)	Mean	4.38	4.30	4.69	4.88
	SD	0.57	0.72	0.76	0.80
	SE	0.26	0.36	0.38	0.33
	N	5	4	4	5
Chloride (mmol/L)	Mean	108.63	109.52	111.07	110.85
	SD	1.01	0.54	2.57	3.64
	SE	0.45	0.32	1.29	1.49
	N	5	4	4	5
Total Cholesterol (mmol/L)	Mean	3.67	4.13	4.51	4.47
	SD	0.64	0.31	1.20	1.05
	SE	0.29	0.40	0.60	0.44
	N	5	4	4	5

Statistical analysis was performed using SAS release 6.12
Significantly different from control: * - 95% confidence level

Group Mean Clinical Chemistry Data CLE Study No.1939-004

Occasion Week 26

b) Female Animals (cont.)

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Triglycerides (mmol/L)	Mean	2.74	1.13	0.95	1.31
	SD	2.77	0.25	0.19	0.36
	SE	1.24	0.12	0.10	0.15
	N	5	4	4	6
Total Protein (g/L)	Mean	83.46	81.20	89.92	85.35
	SD	8.51	2.23	8.60	10.26
	SE	3.81	1.14	4.30	4.19
	N	5	4	4	6
Creatine Kinase (U/L)	Mean	240.16	177.88	583.19	196.18
	SD	137.18	83.54	547.46	77.08
	SE	61.35	41.77	273.73	31.47
	N	5	4	4	6
Albumin (g/L)	Mean	55.14	53.02	54.24	51.80
	SD	7.44	2.41	4.62	7.07
	SE	3.33	1.21	2.31	2.89
	N	5	4	4	6
Globulin (g/L)	Mean	28.32	28.17	35.68	34.15
	SD	3.05	2.85	10.82	7.32
	SE	1.36	1.42	5.41	3.23
	N	5	4	4	6
A/G Ratio	Mean	1.96	1.90	1.62	1.58
	SD	0.32	0.25	0.45	0.37
	SE	0.14	0.13	0.23	0.15
	N	5	4	4	6

Statistical analysis was performed using SAS release 6.12

Group Mean Clinical Chemistry Data CLE Study No.1939-004

Occasion Week 26

b) Female Animals (cont.)

Protein Electrophoresis Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Albumin (%)	Mean	63.2	63.9	58.8	58.8
	SD	2.1	3.6	6.6	4.2
	SE	0.9	1.8	3.3	1.7
	N	5	4	4	6
Alpha1-Globulin (%)	Mean	3.5	2.8	2.8	2.9
	SD	0.4	0.3	0.8	0.8
	SE	0.2	0.2	0.4	0.3
	N	5	4	4	6
Alpha2-Globulin (%)	Mean	8.8	9.3	9.5	9.6
	SD	0.7	0.7	2.0	1.0
	SE	0.3	0.3	1.0	0.4
	N	5	4	4	6
Beta Globulin (%)	Mean	10.9	10.4	9.8	10.9
	SD	1.4	1.5	1.2	1.3
	SE	0.6	0.8	0.6	0.5
	N	5	4	4	6
Gamma Globulin (%)	Mean	13.7	13.2	19.1	17.9
	SD	3.7	2.1	9.0	5.3
	SE	1.6	1.1	4.5	2.2
	N	5	4	4	6
A/G Ratio	Mean	1.72	1.79	1.47	1.45
	SD	0.15	0.28	0.36	0.24
	SE	0.07	0.14	0.18	0.10
	N	5	4	4	6

Statistical analysis was performed using SAS release 6.12

Urinalysis: No treatment-related effects during the Treatment and Recovery phases; the results (group means) of the urinalysis assessments at the end of the treatment period, provided by the Applicant are presented below:

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Group Mean Urine Analysis Data CLB Study No.1939-004

Occasion Week 26

a) Male Animals

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Volume (mL)	Mean	7.2	8.1	5.0	5.3
	SD	4.6	2.1	2.7	1.4
	SE	1.9	1.0	1.3	0.6
	N	6	4	4	5
Specific Gravity	Mean	1.007	1.007	1.010	1.009
	SD	0.006	0.004	0.004	0.005
	SE	0.002	0.002	0.002	0.002
	N	6	4	4	5

Group Mean Urine Analysis Data CLB Study No.1939-004

Occasion Week 26

b) Female Animals

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Volume (mL)	Mean	4.8	3.6	6.3	3.1
	SD	3.0	4.1	3.7	1.2
	SE	1.3	2.1	1.9	0.5
	N	5	4	4	6
Specific Gravity	Mean	1.025	1.020	1.017	1.017
	SD	0.009	0.005	0.006	0.010
	SE	0.004	0.002	0.003	0.004
	N	5	4	4	6

Male Hormone Analysis: No treatment-related effects during the Treatment and Recovery phases; the results (group means) of the male hormone analyses provided by the Applicant are presented below:

Group Mean Hormone Analysis Data CLB Study No.1939-004

Testosterone (nmol/L)

Occasion		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Pre-dose -2	Mean	59.56	8.60	21.57	44.71
	SD	66.99	10.01	28.46	50.54
	SE	27.35	5.00	14.23	20.63
	N	6	4	4	6
Pre-dose -1	Mean	47.59	22.64	4.25	12.21
	SD	60.71	21.97	3.36	9.86
	SE	24.78	10.99	1.68	4.03
	N	6	4	4	5
Week 14	Mean	31.64	12.14	23.89	15.79
	SD	38.74	14.96	37.33	25.32
	SE	15.82	7.48	18.66	10.34
	N	6	4	4	5
Week 25	Mean	30.60	24.28	25.40	24.00
	SD	52.32	25.09	41.16	30.23
	SE	21.36	12.55	20.58	12.34
	N	6	4	4	5
Week 31	Mean	38.35			26.60
	SD	-			-
	SE	-			-
	N	2			2

Standard deviation and standard error not calculated for less than three values

Statistical analysis was performed using SAS release 6.12

Organ weights: No treatment-related effects at the end of the Treatment and Recovery phases; the results of the organ weight measurements as a measure of absolute weight, relative to brain weight, and relative to body weight at the end of the treatment period (group means) provided by the Applicant are presented below:

Group Mean Organ Weights (g) CLE Study No. 1939-004

Terminal Kill

a) Male Animals

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Body Weight at Necropsy (g)	Mean	354.4	361.5	379.0	366.0
	SD	34.9	74.8	35.8	32.0
	SE	17.5	37.4	17.9	16.0
	N	4	4	4	4
Spleen	Mean	0.41	0.45	0.34	0.50
	SD	0.10	0.11	0.06	0.13
	SE	0.05	0.05	0.03	0.06
	N	4	4	4	4
Adrenal left	Mean	0.04	0.05	0.05	0.04
	SD	0.01	0.02	0.01	0.01
	SE	0.00	0.01	0.00	0.00
	N	4	4	4	4
Adrenal right	Mean	0.03	0.05	0.04	0.04
	SD	0.01	0.01	0.01	0.01
	SE	0.00	0.01	0.00	0.00
	N	4	4	4	4
Adrenals total	Mean	0.07	0.10	0.09	0.07
	SD	0.02	0.03	0.02	0.01
	SE	0.01	0.01	0.01	0.01
	N	4	4	4	4
Kidney left	Mean	0.92	1.05	0.93	0.94
	SD	0.16	0.20	0.14	0.20
	SE	0.08	0.10	0.07	0.10
	N	4	4	4	4
Kidney right	Mean	0.92	1.01	0.99	0.96
	SD	0.19	0.20	0.16	0.14
	SE	0.10	0.10	0.08	0.07
	N	4	4	4	4
Kidneys total	Mean	1.84	2.07	1.92	1.90
	SD	0.35	0.39	0.30	0.33
	SE	0.17	0.20	0.15	0.17
	N	4	4	4	4

Statistical analysis was performed using SAS release 6.12

Group Mean Organ Weights (g) CLE Study No. 1939-004

Terminal Kill

3) Male Animals (cont.)

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Liver	Mean	10.27	12.63	11.16	11.16
	SD	1.35	5.48	1.72	2.49
	SE	0.67	3.24	0.86	1.25
	N	4	4	4	4
Testis left	Mean	0.57	0.48	0.62	0.64
	SD	0.10	0.04	0.06	0.09
	SE	0.05	0.02	0.03	0.05
	N	4	4	4	4
Testis right	Mean	0.59	0.49	0.62	0.64
	SD	0.13	0.04	0.07	0.09
	SE	0.06	0.02	0.04	0.04
	N	4	4	4	4
Testes total	Mean	1.16	0.97	1.23	1.23
	SD	0.22	0.08	0.13	0.17
	SE	0.11	0.04	0.06	0.09
	N	4	4	4	4
Epididymis left	Mean	0.11	0.10	0.13	0.09
	SD	0.01	0.02	0.04	0.03
	SE	0.00	0.01	0.02	0.01
	N	4	4	4	4
Epididymis right	Mean	0.10	0.09	0.12	0.10
	SD	0.02	0.01	0.02	0.04
	SE	0.01	0.01	0.01	0.02
	N	4	4	4	4
Epididymides total	Mean	0.21	0.19	0.24	0.19
	SD	0.02	0.02	0.06	0.05
	SE	0.01	0.01	0.03	0.03
	N	4	4	4	4
Seminal vesicles	Mean	0.19	0.15	0.19	0.15
	SD	0.06	0.06	0.08	0.07
	SE	0.03	0.03	0.04	0.04
	N	4	4	4	4

Statistical analysis was performed using SAS release 6.12

Group Mean Organ Weights (g) CLE Study No. 1939-004

Terminal Kill

3) Male Animals (cont.)

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Prostate	Mean	0.18	0.15	0.22	0.18
	SD	0.03	0.03	0.07	0.05
	SE	0.01	0.01	0.04	0.02
	N	4	4	4	4
Thyroid (with Parathyroids)	Mean	0.11	0.12	0.09	0.15
	SD	0.04	0.03	0.05	0.10
	SE	0.02	0.01	0.02	0.05
	N	4	4	4	4
Heart	Mean	2.17	2.29	2.24	2.31
	SD	0.18	0.37	0.36	0.35
	SE	0.09	0.19	0.18	0.18
	N	4	4	4	4
Brain	Mean	8.18	8.06	7.90	8.07
	SD	0.29	0.60	0.57	0.63
	SE	0.14	0.30	0.29	0.32
	N	4	4	4	4
Pituitary	Mean	0.012	0.010	0.011	0.012
	SD	0.001	0.002	0.002	0.002
	SE	0.001	0.001	0.001	0.001
	N	4	4	4	4

Statistical analysis was performed using SAS release 6.12

Group Mean Organ Weights (g) CLE Study No. 1939-004

Terminal Kill

b) Female Animals

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Body Weight at Necropsy (g)	Mean	345.9	371.1	349.4	359.3
	SD	38.4	46.8	36.3	26.4
	SE	22.1	26.4	18.2	13.2
	N	3	4	4	4
Spleen	Mean	0.63	0.53	0.68	0.40
	SD	0.15	0.14	0.14	0.25
	SE	0.09	0.07	0.07	0.13
	N	3	4	4	4
Adrenal left	Mean	0.06	0.07	0.06	0.07
	SD	0.01	0.01	0.03	0.02
	SE	0.00	0.01	0.01	0.01
	N	3	4	4	4
Adrenal right	Mean	0.05	0.05	0.05	0.05
	SD	0.01	0.02	0.01	0.02
	SE	0.00	0.01	0.00	0.01
	N	3	4	4	4
Adrenals total	Mean	0.11	0.12	0.11	0.13
	SD	0.01	0.02	0.03	0.04
	SE	0.00	0.01	0.01	0.02
	N	3	4	4	4
Kidney left	Mean	0.91	1.05	0.92	1.06
	SD	0.16	0.12	0.12	0.21
	SE	0.09	0.06	0.06	0.11
	N	3	4	4	4
Kidney right	Mean	0.95	1.05	0.97	1.06
	SD	0.19	0.05	0.15	0.31
	SE	0.11	0.03	0.08	0.15
	N	3	4	4	4
Kidneys total	Mean	1.85	2.10	1.89	2.13
	SD	0.35	0.15	0.28	0.51
	SE	0.20	0.07	0.14	0.25
	N	3	4	4	4

Statistical analysis was performed using SAS release 6.12

Group Mean Organ Weights (g) CLE Study No. 1939-004

Terminal Kill

b) Female Animals (cont.)

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Liver	Mean	11.98	13.08	11.12	13.25
	SD	3.69	1.41	0.88	3.99
	SE	2.13	0.70	0.44	1.99
	N	3	4	4	4
Ovary left	Mean	0.06	0.09	0.07	0.09
	SD	0.02	0.07	0.03	0.06
	SE	0.01	0.03	0.01	0.03
	N	3	4	4	4
Ovary right	Mean	0.06	0.10	0.08	0.08
	SD	0.02	0.07	0.03	0.04
	SE	0.01	0.03	0.02	0.02
	N	3	4	4	4
Ovaries total	Mean	0.12	0.19	0.15	0.17
	SD	0.03	0.14	0.05	0.08
	SE	0.02	0.07	0.03	0.04
	N	3	4	4	4
Thyroid (with Parathyroids)	Mean	0.13	0.18	0.15	0.21
	SD	0.03	0.06	0.05	0.13
	SE	0.02	0.03	0.03	0.07
	N	3	4	4	4
Heart	Mean	1.77	2.12	1.97	2.08
	SD	0.26	0.38	0.11	0.39
	SE	0.15	0.19	0.05	0.20
	N	3	4	4	4
Brain	Mean	8.11	8.13	7.96	8.31
	SD	0.54	0.21	0.70	0.27
	SE	0.31	0.11	0.35	0.14
	N	3	4	4	4
Pituitary	Mean	0.010	0.011	0.013	0.011
	SD	0.004	0.003	0.002	0.001
	SE	0.002	0.001	0.001	0.000
	N	3	4	4	4

Statistical analysis was performed using SAS release 6.12

Group Mean Organ/Body Weight Ratios (%) CLE Study No. 1939-004

Terminal Kill

3) Male Animals

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Body Weight at Necropsy (g)	Mean	364.4	361.5	370.0	366.0
	SD	34.9	74.9	35.8	32.0
	SE	17.5	37.4	17.9	16.0
	N	4	4	4	4
Spleen	Mean	0.12	0.12	0.09	0.13
	SD	0.02	0.01	0.01	0.02
	SE	0.01	0.00	0.01	0.01
	N	4	4	4	4
Adrenal left	Mean	0.01	0.02	0.01	0.01
	SD	0.00	0.01	0.00	0.00
	SE	0.00	0.00	0.00	0.00
	N	4	4	4	4
Adrenal right	Mean	0.01	0.01	0.01	0.01
	SD	0.00	0.00	0.00	0.00
	SE	0.00	0.00	0.00	0.00
	N	4	4	4	4
Adrenals total	Mean	0.02	0.03	0.02	0.02
	SD	0.00	0.01	0.00	0.00
	SE	0.00	0.00	0.00	0.00
	N	4	4	4	4
Kidney left	Mean	0.26	0.29	0.25	0.25
	SD	0.03	0.02	0.02	0.03
	SE	0.01	0.01	0.01	0.02
	N	4	4	4	4
Kidney right	Mean	0.26	0.28	0.27	0.25
	SD	0.03	0.01	0.02	0.01
	SE	0.02	0.00	0.01	0.01
	N	4	4	4	4
Kidneys total	Mean	0.52	0.57	0.52	0.52
	SD	0.06	0.03	0.03	0.04
	SE	0.03	0.01	0.02	0.02
	N	4	4	4	4

Statistical analysis was performed using SAS release 6.12

Group Mean Organ/Body Weight Ratios (%) CLE Study No. 1939-004

Terminal Kill

a) Male Animals (cont.)

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Liver	Mean	2.69	3.35	3.00	3.02
	SD	0.17	0.96	0.19	0.39
	SE	0.09	0.48	0.09	0.20
	N	4	4	4	4
Testis left	Mean	0.16	0.14	0.17	0.17
	SD	0.02	0.02	0.01	0.01
	SE	0.01	0.01	0.00	0.01
	N	4	4	4	4
Testis right	Mean	0.17	0.14	0.17	0.18
	SD	0.02	0.02	0.01	0.01
	SE	0.01	0.01	0.00	0.01
	N	4	4	4	4
Testes total	Mean	0.33	0.27	0.33	0.35
	SD	0.04	0.04	0.01	0.02
	SE	0.02	0.02	0.00	0.01
	N	4	4	4	4
Epididymis left	Mean	0.03	0.03	0.03	0.03
	SD	0.00	0.01	0.01	0.01
	SE	0.00	0.00	0.00	0.00
	N	4	4	4	4
Epididymis right	Mean	0.03	0.02	0.03	0.03
	SD	0.01	0.01	0.01	0.01
	SE	0.00	0.00	0.00	0.01
	N	4	4	4	4
Epididymides total	Mean	0.06	0.05	0.07	0.05
	SD	0.01	0.01	0.01	0.02
	SE	0.01	0.01	0.01	0.01
	N	4	4	4	4
Seminal vesicles	Mean	0.05	0.05	0.05	0.04
	SD	0.02	0.02	0.02	0.02
	SE	0.01	0.01	0.01	0.01
	N	4	4	4	4

Statistical analysis was performed using SAS release 6.12

Group Mean Organ/Body Weight Ratios (%) CLE Study No. 1939-004

Terminal Kill

3) Male Animals (cont.)

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Prostate	Mean	0.05	0.04	0.06	0.05
	SD	0.01	0.01	0.02	0.01
	SE	0.00	0.01	0.01	0.01
	N	4	4	4	4
Thyroid (with Parathyroids)	Mean	0.03	0.03	0.02	0.04
	SD	0.01	0.00	0.01	0.02
	SE	0.00	0.00	0.01	0.01
	N	4	4	4	4
Heart	Mean	0.61	0.64	0.60	0.63
	SD	0.03	0.06	0.05	0.08
	SE	0.01	0.03	0.02	0.04
	N	4	4	4	4
Brain	Mean	2.32	2.27	2.14	2.22
	SD	0.22	0.23	0.10	0.25
	SE	0.11	0.14	0.05	0.12
	N	4	4	4	4
Pituitary	Mean	0.003	0.003	0.003	0.003
	SD	0.001	0.001	0.001	0.001
	SE	0.000	0.000	0.000	0.000
	N	4	4	4	4

Statistical analysis was performed using SAS release 6.12

Group Mean Organ/Body Weight Ratios (%) CLE Study No. 1939-004

Terminal Kill

b) Female Animals

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Body Weight at Necropsy (g)	Mean	345.9	371.1	349.4	359.3
	SD	33.4	40.8	36.3	26.4
	SE	22.1	20.4	18.2	13.2
	N	3	4	4	4
Spleen	Mean	0.19	0.15	0.20	0.11
	SD	0.07	0.05	0.06	0.07
	SE	0.04	0.03	0.03	0.03
	N	3	4	4	4
Adrenal left	Mean	0.02	0.02	0.02	0.02
	SD	0.00	0.00	0.01	0.01
	SE	0.00	0.00	0.00	0.00
	N	3	4	4	4
Adrenal right	Mean	0.02	0.01	0.01	0.02
	SD	0.00	0.00	0.00	0.00
	SE	0.00	0.00	0.00	0.00
	N	3	4	4	4
Adrenals total	Mean	0.03	0.03	0.03	0.03
	SD	0.00	0.00	0.01	0.01
	SE	0.00	0.00	0.00	0.00
	N	3	4	4	4
Kidney left	Mean	0.26	0.29	0.26	0.29
	SD	0.02	0.04	0.01	0.04
	SE	0.01	0.02	0.01	0.02
	N	3	4	4	4
Kidney right	Mean	0.27	0.23	0.28	0.29
	SD	0.03	0.02	0.02	0.05
	SE	0.02	0.01	0.01	0.03
	N	3	4	4	4
Kidneys total	Mean	0.53	0.57	0.54	0.59
	SD	0.04	0.06	0.03	0.10
	SE	0.03	0.03	0.01	0.05
	N	3	4	4	4

Statistical analysis was performed using SAS release 6.12

Group Mean Organ/Body Weight Ratios (%) CLE Study No. 1939-004

Terminal Kill

b) Female Animals (cont.)

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Liver	Mean	3.43	3.54	3.19	3.65
	SD	0.81	0.43	0.15	0.85
	SE	0.47	0.21	0.08	0.42
	N	3	4	4	4
Ovary left	Mean	0.02	0.02	0.02	0.03
	SD	0.00	0.02	0.01	0.02
	SE	0.00	0.01	0.00	0.01
	N	3	4	4	4
Ovary right	Mean	0.02	0.03	0.02	0.02
	SD	0.00	0.02	0.01	0.01
	SE	0.00	0.01	0.00	0.01
	N	3	4	4	4
Ovaries total	Mean	0.03	0.05	0.04	0.05
	SD	0.01	0.04	0.01	0.02
	SE	0.00	0.02	0.01	0.01
	N	3	4	4	4
Thyroid (with Parathyroids)	Mean	0.04	0.05	0.04	0.05
	SD	0.01	0.01	0.01	0.04
	SE	0.01	0.01	0.01	0.02
	N	3	4	4	4
Heart	Mean	0.51	0.57	0.57	0.57
	SD	0.05	0.11	0.05	0.03
	SE	0.03	0.05	0.02	0.04
	N	3	4	4	4
Brain	Mean	2.37	2.22	2.29	2.33
	SD	0.42	0.22	0.19	0.22
	SE	0.24	0.11	0.09	0.11
	N	3	4	4	4
Pituitary	Mean	0.003	0.003	0.004	0.003
	SD	0.001	0.001	0.000	0.000
	SE	0.001	0.001	0.000	0.000
	N	3	4	4	4

Statistical analysis was performed using SAS release 6.12

Group Mean Organ/Brain Weight Ratios (%) CLE Study No. 1939-004

Terminal Kill

a) Male Animals

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Brain Weight (g)	Mean	8.18	8.05	7.90	8.07
	SD	0.29	0.60	0.57	0.63
	SE	0.14	0.30	0.29	0.32
	N	4	4	4	4
Spleen	Mean	5.01	5.47	4.23	6.25
	SD	1.19	0.95	0.78	1.92
	SE	0.60	0.48	0.39	0.96
	N	4	4	4	4
Adrenal left	Mean	0.49	0.66	0.60	0.47
	SD	0.10	0.23	0.08	0.12
	SE	0.05	0.12	0.04	0.06
	N	4	4	4	4
Adrenal right	Mean	0.40	0.62	0.54	0.44
	SD	0.12	0.14	0.13	0.08
	SE	0.06	0.07	0.06	0.04
	N	4	4	4	4
Adrenals total	Mean	0.89	1.28	1.14	0.90
	SD	0.21	0.37	0.17	0.19
	SE	0.11	0.18	0.08	0.09
	N	4	4	4	4
Kidney left	Mean	11.24	13.01	11.77	11.72
	SD	1.91	1.65	1.17	2.93
	SE	0.95	0.83	0.58	1.47
	N	4	4	4	4
Kidney right	Mean	11.25	12.50	12.47	11.93
	SD	2.35	1.55	1.31	2.04
	SE	1.18	0.77	0.65	1.02
	N	4	4	4	4
Kidneys total	Mean	22.49	25.50	24.24	23.65
	SD	4.18	3.17	2.47	4.97
	SE	2.09	1.58	1.23	2.48
	N	4	4	4	4

Statistical analysis was performed using SAS release 6.12

Group Mean Organ/Brain Weight Ratios (%) CLE Study No. 1939-004

Terminal Kill

3) Male Animals (cont.)

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Liver	Mean	135.44	153.54	140.94	139.19
	SD	14.60	67.74	14.36	35.19
	SE	7.30	33.87	7.18	17.60
	N	4	4	4	4
Testis left	Mean	6.93	6.00	7.79	7.90
	SD	1.17	0.54	0.42	1.23
	SE	0.58	0.27	0.21	0.62
	N	4	4	4	4
Testis right	Mean	7.23	6.09	7.60	8.02
	SD	1.45	0.41	0.37	1.45
	SE	0.72	0.21	0.18	0.73
	N	4	4	4	4
Testes total	Mean	14.16	12.10	15.59	15.92
	SD	2.57	0.93	0.61	2.63
	SE	1.28	0.47	0.31	1.32
	N	4	4	4	4
Epididymis left	Mean	1.34	1.23	1.57	1.14
	SD	0.06	0.27	0.43	0.32
	SE	0.03	0.13	0.21	0.16
	N	4	4	4	4
Epididymis right	Mean	1.26	1.05	1.46	1.19
	SD	0.28	0.18	0.30	0.38
	SE	0.14	0.09	0.16	0.19
	N	4	4	4	4
Epididymides total	Mean	2.60	2.35	3.03	2.32
	SD	0.24	0.37	0.58	0.65
	SE	0.12	0.19	0.29	0.33
	N	4	4	4	4
Seminal vesicles	Mean	2.28	2.01	2.43	1.93
	SD	0.69	0.67	0.96	0.94
	SE	0.34	0.34	0.48	0.47
	N	4	4	4	4

Statistical analysis was performed using SAS release 6.12

Group Mean Organ/Brain Weight Ratios (%) CLE Study No. 1939-004

Terminal Kill

a) Male Animals (cont.)

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Prostate	Mean	2.15	1.84	2.71	2.25
	SD	0.36	0.36	0.85	0.62
	SE	0.18	0.18	0.43	0.31
	N	4	4	4	4
Thyroid (with Parathyroids)	Mean	1.31	1.42	1.05	1.82
	SD	0.52	0.27	0.53	1.30
	SE	0.26	0.13	0.26	0.65
	N	4	4	4	4
Heart	Mean	26.54	23.35	23.29	28.84
	SD	2.56	3.14	3.26	5.89
	SE	1.28	1.57	1.63	2.94
	N	4	4	4	4
Pituitary	Mean	0.147	0.119	0.140	0.143
	SD	0.014	0.029	0.029	0.024
	SE	0.007	0.015	0.015	0.012
	N	4	4	4	4

Statistical analysis was performed using SAS release 6.12

Group Mean Organ/Brain Weight Ratios (%) CLE Study No. 1939-004

Terminal Kill

b) Female Animals

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Brain Weight (g)	Mean	8.11	8.18	7.98	8.31
	SD	0.54	0.21	0.70	0.27
	SE	0.31	0.11	0.35	0.14
	N	3	4	4	4
Spleen	Mean	7.70	6.43	8.59	4.83
	SD	1.55	1.75	2.36	3.25
	SE	0.90	0.88	1.18	1.63
	N	3	4	4	4
Adrenal left	Mean	0.70	0.82	0.74	0.82
	SD	0.09	0.14	0.27	0.30
	SE	0.05	0.07	0.14	0.15
	N	3	4	4	4
Adrenal right	Mean	0.70	0.67	0.60	0.70
	SD	0.11	0.22	0.03	0.22
	SE	0.06	0.11	0.02	0.11
	N	3	4	4	4
Adrenals total	Mean	1.40	1.30	1.34	1.51
	SD	0.17	0.15	0.26	0.51
	SE	0.10	0.09	0.13	0.26
	N	3	4	4	4
Kidney left	Mean	11.28	12.86	11.52	12.83
	SD	2.60	1.29	1.05	2.83
	SE	1.50	0.65	0.53	1.42
	N	3	4	4	4
Kidney right	Mean	11.80	12.81	12.17	12.85
	SD	3.01	0.50	1.45	3.91
	SE	1.74	0.25	0.72	1.96
	N	3	4	4	4
Kidneys total	Mean	23.09	25.67	23.69	25.67
	SD	5.60	1.42	2.50	6.65
	SE	3.23	0.71	1.25	3.32
	N	3	4	4	4

Statistical analysis was performed using SAS release 6.12

Group Mean Organ/Brain Weight Ratios (%) CLE Study No. 1939-004

Terminal Kill

b) Female Animals (cont.)

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Liver	Mean	150.20	159.77	139.64	160.15
	SD	56.83	13.71	5.79	51.01
	SE	32.81	6.85	2.90	25.51
	N	3	4	4	4
Ovary left	Mean	0.71	1.09	0.87	1.08
	SD	0.23	0.82	0.27	0.70
	SE	0.13	0.41	0.14	0.35
	N	3	4	4	4
Ovary right	Mean	0.75	1.18	0.93	0.93
	SD	0.26	0.81	0.30	0.48
	SE	0.15	0.40	0.15	0.24
	N	3	4	4	4
Ovaries total	Mean	1.45	2.27	1.80	2.00
	SD	0.45	1.62	0.53	0.98
	SE	0.26	0.81	0.27	0.49
	N	3	4	4	4
Thyroid (with Parathyroids)	Mean	1.60	2.13	1.68	2.49
	SD	0.26	0.68	0.51	1.35
	SE	0.15	0.34	0.26	0.73
	N	3	4	4	4
Heart	Mean	22.03	25.80	24.61	25.08
	SD	4.74	4.02	0.86	5.43
	SE	2.74	2.01	0.43	2.72
	N	3	4	4	4
Pituitary	Mean	0.127	0.129	0.161	0.133
	SD	0.039	0.034	0.024	0.012
	SE	0.023	0.017	0.012	0.006
	N	3	4	4	4

Statistical analysis was performed using SAS release 6.12

Flow cytometry of testicular tissue: No treatment-related effects at the end of the treatment period

Group Mean Flow Cytometric Data CLE Study No. 1939-004

Testicular Tissue - Occasion at necropsy

Terminal Kill

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Left Testis HC (%)	Mean	7.93	6.46	7.38	5.64
	SD	1.27	1.90	1.94	1.32
	SE	0.63	0.95	0.97	0.66
	N	4	4	4	4
Left Testis 1C (%)	Mean	36.63	38.48	35.52	37.52
	SD	4.00	4.75	3.59	2.20
	SE	2.00	2.37	1.79	1.10
	N	4	4	4	4
Left Testis 2C (%)	Mean	13.97	14.67	13.86	13.73
	SD	1.18	1.83	1.15	0.90
	SE	0.59	0.92	0.58	0.45
	N	4	4	4	4
Left Testis s-ph (%)	Mean	5.00	4.70	4.45	4.58
	SD	0.47	0.95	0.47	0.92
	SE	0.24	0.47	0.24	0.46
	N	4	4	4	4
Left Testis 4C (%)	Mean	13.92	14.93	15.46	15.99
	SD	1.59	2.46	2.80	1.45
	SE	0.79	1.23	1.40	0.73
	N	4	4	4	4
Left Testis Debris (%)	Mean	22.55	20.73	23.34	22.50
	SD	4.31	1.68	1.11	2.34
	SE	2.15	0.84	0.55	1.17
	N	4	4	4	4

Statistical Analysis was performed using SAS release 6.12

APPEARS THIS WAY ON ORIGINAL

Group Mean Flow Cytometric Data CLE Study No. 1939-004

Testicular Tissue - Occasion at necropsy

Terminal Kill

(cont.)

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Right Testis HC (%)	Mean	7.74	6.26	6.98	8.15
	SD	1.01	2.26	0.87	3.01
	SE	0.50	1.13	0.43	1.50
	N	4	4	4	4
Right Testis 1C (%)	Mean	38.56	37.62	34.80	36.31
	SD	3.35	3.63	2.54	3.35
	SE	1.67	1.81	1.32	1.68
	N	4	4	4	4
Right Testis 2C (%)	Mean	13.48	14.38	15.22	13.65
	SD	1.41	0.49	1.93	1.18
	SE	0.70	0.24	0.97	0.59
	N	4	4	4	4
Right Testis s-ph (%)	Mean	4.38	5.85	5.16	5.25
	SD	0.67	2.36	0.41	1.61
	SE	0.34	1.18	0.20	0.80
	N	4	4	4	4
Right Testis 4C (%)	Mean	13.89	13.79	15.65	14.51
	SD	1.40	1.23	2.18	2.82
	SE	0.70	0.62	1.09	1.41
	N	4	4	4	4
Right Testis Debris (%)	Mean	21.96	22.11	22.09	22.14
	SD	4.14	2.18	1.85	2.73
	SE	2.07	1.09	0.92	1.36
	N	4	4	4	4

Statistical Analysis was performed using SAS release 6.12

Sponsor Reference No. 050070 Summary Tables Page

Group Mean Flow Cytometric Data CLE Study No. 1939-004

Testicular Tissue - Occasion at necropsy

Terminal Kill

(cont.)

Parameter		Group 1 0 mg/kg/ twice weekly	Group 2 10 mg/kg/ twice weekly	Group 3 30 mg/kg/ twice weekly	Group 4 100 mg/kg/ twice weekly
Mean of	Mean	7.84	6.36	7.18	5.89
Left and	SD	0.92	1.68	1.33	1.57
Right Testis	SE	0.46	0.84	0.66	0.78
HC (%)	N	4	4	4	4
Mean of	Mean	37.60	38.85	35.21	36.92
Left and	SD	3.60	3.52	3.07	2.62
Right Testis	SE	1.80	1.76	1.53	1.31
1C (%)	N	4	4	4	4
Mean of	Mean	13.72	14.52	14.54	13.71
Left and	SD	1.08	1.08	1.35	0.88
Right Testis	SE	0.54	0.54	0.67	0.44
2C (%)	N	4	4	4	4
Mean of	Mean	4.69	5.27	4.30	4.91
Left and	SD	0.34	1.47	0.26	1.23
Right Testis	SE	0.17	0.74	0.13	0.62
s-ph (%)	N	4	4	4	4
Mean of	Mean	13.90	14.35	15.55	15.25
Left and	SD	1.45	1.49	2.12	1.84
Right Testis	SE	0.73	0.74	1.06	0.92
4C (%)	N	4	4	4	4
Mean of	Mean	22.35	21.44	22.71	22.32
Left and	SD	3.59	1.75	1.44	2.41
Right Testis	SE	1.80	0.87	0.72	1.21
Debris (%)	N	4	4	4	4

Statistical Analysis was performed using SAS release 6.12

Gross pathology: No treatment-related effects at the end of the Treatment and Recovery phases; the results of the necroscopic examination provided by the Applicant, are presented below:

GROUP INCIDENCE: NECROPSY - ALL DATA

Kill type: Terminal

Tissue / Observation	Group:	1	2	3	4	1	2	3	4
	Sex:	M	M	M	M	F	F	F	F
	Number:	4	4	4	4	3	4	4	4
Adrenal									
Cyst		0	0	0	0	0	1	0	0
Injection site									
Haematoma		0	0	0	1	0	0	0	0
Liver									
Prominent vessels		0	0	1	0	0	0	0	0
Lung									
Discoloured focus		0	0	1	0	0	0	0	0
Mandibular lymph node									
Red		3	3	3	2	0	1	2	2
Mesenteric lymph node									
Red		3	2	2	3	0	2	1	0
Spleen									
Discoloured focus		0	0	0	0	0	0	0	1
Thymus									
Red		1	2	0	1	1	0	1	0
Thyroid									
Large		0	0	0	1	0	0	0	0

Kill type: Recovery

Tissue / Observation	Group:	1	4	1	4
	Sex:	M	M	F	F
	Number:	2	2	2	2
Femur + marrow					
Pale		0	0	0	1
Knee joint					
Deformity		0	0	0	1
Mandibular lymph node					
Red		0	1	0	0
Mesenteric lymph node					
Large		0	1	0	0

Histopathology: No treatment-related effects at the end of the Treatment and Recovery phases; the results of the microscopic examinations provided by the Applicant, are presented below:

GROUP INCIDENCE: HISTOPATHOLOGY - ALL DATA

Kill type: Terminal

Tissue / Observation	Group:	1	2	3	4	1	2	3	4
	Sex:	M	M	M	M	F	F	F	F
	Number:	4	4	4	4	3	4	4	4
Adrenal									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		0	0	0	0	1	0	0	1
Dilatation		0	0	0	0	0	0	0	1
Fatty vacuolation		2	3	3	1	1	1	1	0
Cortical vacuolation		1	0	0	0	1	0	0	0
Haemopoiesis		3	2	3	4	0	4	2	3
Inflammatory cell foci		0	1	1	0	0	0	1	0
Hypertrophy		1	2	2	0	0	0	0	0
Aorta									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		4	4	4	4	2	3	3	4
Mineralization		0	0	0	0	1	1	1	0
Intimal proliferation		0	0	0	0	0	1	0	0
Brain									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		4	4	4	4	3	4	3	4
Haemopoiesis		0	0	0	0	0	0	1	0
Caecum									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		4	4	3	4	3	3	4	4
Inflammation		0	0	0	0	0	1	0	0
Inflammatory cell infiltration		0	0	1	0	0	0	0	0
Colon									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		4	4	4	4	3	3	4	4
Inflammation		0	0	0	0	0	1	0	0
Duodenum									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		3	3	2	3	0	1	1	1
Dilated Brunner's glands		1	1	2	1	3	3	3	3
Epididymis									
Number examined		4	4	4	4	-	-	-	-
Not remarkable		4	4	4	4	-	-	-	-
Eye									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		4	4	4	4	3	4	4	4
Gall bladder									
Number examined		4	4	4	4	3	3	4	4
Not remarkable		4	4	4	4	3	3	2	4
Inflammation		0	0	0	0	0	1	2	0
Heart									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		1	2	2	2	3	3	4	0
Degeneration		0	1	0	0	0	0	0	0
Mineralization		0	0	0	0	0	1	0	0
Haemorrhage		0	1	0	0	0	0	0	0
Inflammation		0	0	1	0	0	0	0	0
Inflammatory cell foci		1	2	1	2	0	1	0	4
Fibrosis		1	0	0	2	0	1	0	0

GROUP INCIDENCE: HISTOPATHOLOGY - ALL DATA

Kill type: Terminal

Tissue / Observation	Group:	1	2	3	4	1	2	3	4
	Sex:	M	M	M	M	F	F	F	F
	Number:	4	4	4	4	3	4	4	4
Heart (continued)									
Osseous metaplasia		1	0	0	0	0	0	0	0
Injection site arm									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		0	0	0	0	0	1	1	0
Degeneration		2	0	0	0	0	0	0	0
Necrosis		0	1	1	2	0	2	1	0
Hemorrhage		4	4	4	4	3	3	3	4
Inflammation		1	1	1	2	0	1	0	2
Fibrosis		3	2	3	1	3	3	2	1
Phlebitis/periphlebitis		3	2	2	0	2	3	1	3
Ileum									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		4	3	4	4	3	3	4	4
Inflammatory cell foci		0	0	0	0	0	1	0	0
Crypt microabscess		0	1	0	0	0	0	0	0
Injection site leg									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		2	1	2	3	0	3	2	2
Degeneration		1	0	0	0	0	0	0	0
Necrosis		0	0	1	0	0	0	1	0
Hemorrhage		2	3	2	1	3	1	2	2
Thrombus		0	0	0	0	1	0	0	0
Fibrosis		1	1	1	0	1	1	2	1
Phlebitis/periphlebitis		0	0	1	0	1	0	1	1
Jejunum									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		4	4	4	4	3	4	4	4
Kidney									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		0	1	0	0	0	0	0	0
Cystic tubules		0	0	0	1	1	0	0	0
Tubular dilatation		0	0	0	2	0	0	0	1
Basophilic tubules		1	2	1	2	0	0	1	1
Casts		0	0	0	1	0	0	0	1
Cortical mineralization		0	0	0	1	0	0	0	0
Papillary mineralization		0	0	0	2	0	1	0	0
Inflammatory cell foci		4	3	4	3	3	4	4	4
Inflammatory cell infiltration		0	0	0	0	0	0	1	0
Fibrosis		0	1	0	0	0	1	0	1
Tubular pigment		2	3	2	3	1	3	2	1
Tubular hyperplasia		0	0	0	0	0	0	0	1
Liver									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		0	2	0	1	0	1	0	0
Vacuolation		1	0	1	1	0	0	0	1
Hepatocyte vacuolation		0	1	0	0	0	0	0	0
Kupffer cell pigment		0	0	0	0	0	0	0	1
Hemopoiesis		2	1	2	2	1	3	4	3
Inflammatory cell foci		2	0	1	1	0	1	4	0
Inflammatory cell infiltration		0	0	0	0	1	0	0	0
Pigmented histiocytes		0	0	0	0	0	0	1	0
Microgranuloma		2	2	2	2	0	1	0	3

GROUP INCIDENCE: HISTOPATHOLOGY - ALL DATA

Kill type: Terminal

Tissue / Observation	Group:	1	2	3	4	1	2	3	4
	Sex:	M	M	M	M	F	F	F	F
	Number:	4	4	4	4	3	4	3	4
Liver (continued)									
Vasculitis		0	0	0	0	0	0	0	1
Glycogen storage		0	0	0	0	1	0	0	0
Hypertrophy		0	0	0	0	1	0	0	1
Biliary proliferation		0	0	0	0	1	0	0	0
Lung									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		4	4	3	4	3	3	4	4
Unremarkable		0	0	1	0	0	0	0	0
Pleural fibrosis/adhesion		0	0	0	0	0	1	0	0
Mammary gland									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		4	4	3	3	3	4	4	3
Cyst		0	0	1	0	0	0	0	0
Inflammation		0	0	0	0	0	0	0	1
Inflammatory cell foci		0	0	0	1	0	0	0	0
Mandibular lymph node									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		3	1	1	2	3	3	0	2
Unremarkable		1	2	1	1	0	1	0	1
Agonal congestion/haemorrhage		2	1	2	1	0	0	4	1
Mesenteric lymph node									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		3	1	1	1	3	1	2	4
Unremarkable		1	1	0	0	0	1	0	0
Oedema		0	0	0	1	0	0	0	0
Agonal congestion/haemorrhage		2	2	3	2	0	2	2	0
Sinus histiocytosis		0	0	0	1	0	0	0	0
Oesophagus									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		3	4	4	4	3	3	4	4
Inflammation		1	0	0	0	0	1	0	0
Lymphoid hyperplasia		0	0	0	0	0	1	0	0
Optic nerve									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		4	4	4	4	3	4	4	4
Ovary									
Number examined		-	-	-	-	3	4	4	4
Not remarkable		-	-	-	-	3	2	4	3
Cyst		-	-	-	-	0	1	0	0
Foamy histiocytes		-	-	-	-	0	1	0	0
Luteal hyperplasia		-	-	-	-	0	1	0	1
Pancreas									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		4	4	4	4	3	4	4	2
Vacuolation		0	0	0	0	0	0	0	1
Lymphocyte foci		0	0	0	0	0	0	0	1
Pituitary									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		3	4	3	3	2	4	2	3

GROUP INCIDENCE: HISTOPATHOLOGY - ALL DATA

Kill type: Terminal

Tissue / Observation	Group: / Sex: / Number:	1 M 4	2 M 4	3 M 4	4 M 4	1 F 3	2 F 4	3 F 4	4 F 4
Pituitary (continued)									
Cyst		1	0	1	1	1	0	2	0
Pituicyte vacuolation		0	0	0	0	0	0	0	1
Mineralisation		0	0	0	1	0	0	0	0
Parotid									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		3	3	1	2	3	3	1	3
Lymphocyte foci		1	1	3	2	0	1	3	1
Prostate									
Number examined		4	4	4	4	-	-	-	-
Not remarkable		3	3	4	4	-	-	-	-
Mineralisation		1	0	0	0	-	-	-	-
Haemorrhage		0	1	0	0	-	-	-	-
Parathyroid									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		4	4	4	3	3	4	3	4
Cyst		0	0	0	1	0	0	0	0
Lymphocyte foci		0	0	0	0	0	0	1	0
Rectum									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		4	4	4	4	3	3	4	4
Inflammation		0	0	0	0	0	1	0	0
Salivary gland, mandibular									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		4	4	4	4	3	4	4	4
Skin + subcutis									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		4	4	4	4	3	4	4	4
Stomach + marrow									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		3	4	4	4	3	4	3	4
Cyst		0	0	0	0	0	0	1	0
Oedema		1	0	0	0	0	0	0	0
Sciatic nerve									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		2	4	4	3	3	4	3	3
Inflammation		1	0	0	0	0	0	0	0
Inflammatory cell foci		1	0	0	1	0	0	1	1
Spleen									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		4	4	4	4	3	4	4	3
Unremarkable		0	0	0	0	0	0	0	1
Stomach									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		3	4	2	4	3	4	4	3
Vacuolation		0	0	1	0	0	0	0	0
Dilated glands		1	0	2	0	0	0	0	0
Squamous metaplasia		0	0	0	0	0	0	0	1

GROUP INCIDENCE: HISTOPATHOLOGY - ALL DATA

Kill type: Terminal

Tissue / Observation	Group:	1	2	3	4	1	2	3	4
	Sex:	M	M	M	M	F	F	F	F
	Number:	4	4	4	4	3	4	4	4
Skeletal muscle									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		4	4	4	4	3	4	4	4
Seminal vesicle									
Number examined		4	4	4	4	-	-	-	-
Not remarkable		4	4	4	4	-	-	-	-
Spinal cord cervical									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		4	4	4	4	3	4	4	4
Testis									
Number examined		4	4	4	4	-	-	-	-
Not remarkable		3	3	4	3	-	-	-	-
Tubular atrophy		1	1	0	0	-	-	-	-
Oedema		0	0	0	1	-	-	-	-
Thymus									
Number examined		4	4	4	4	3	4	4	3
Not remarkable		3	2	4	3	2	4	3	3
No sample		0	0	0	0	0	0	0	1
Unremarkable		1	2	0	0	1	0	0	0
Cyst		0	0	0	1	0	0	0	0
Agonal congestion/haemorrhage		0	0	0	0	0	0	1	0
Tongue									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		4	4	4	4	3	4	4	4
Trachea									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		4	4	4	4	3	4	4	4
Thyroid									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		3	0	0	0	1	0	0	0
Ectopic thymus		1	0	1	1	3	2	1	1
Follicular distension		3	0	0	3	0	4	0	0
Lymphocyte foci		3	3	0	1	2	1	3	3
Decreased follicular size		0	0	1	0	0	0	0	1
Follicular cell hypertrophy		0	2	0	1	1	0	0	0
C-cell hyperplasia		1	1	3	1	2	3	4	2
Urinary bladder									
Number examined		4	4	4	4	3	4	4	4
Not remarkable		4	4	4	4	3	4	4	4
Uterus									
Number examined		-	-	-	-	3	4	4	4
Not remarkable		-	-	-	-	3	3	3	4
Cyst		-	-	-	-	0	0	1	0
ADENOCARCINOMA		-	-	-	-	0	1	0	0
Vagina									
Number examined		-	-	-	-	3	4	4	4
Not remarkable		-	-	-	-	3	4	4	4

Toxicokinetics:

- Dose-proportional increase in exposure (AUC and Cmax) on Day 1
- Increased exposure in Weeks 11 and 23 vs. Day 1, suggesting accumulation or FcRn receptor saturation
- No gender differences in TK parameters observed
- The results of the TK analysis are presented in the following table (from the original BLA submission):

Table 2-1 Mean toxicokinetic parameters of ACZ885 in serum of marmosets Day 1 of administration

	10 mg/kg				30 mg/kg				100 mg/kg			
Administration Day 1	Males**	SD	Females**	SD	Males***	SD	Females***	SD	Males****	SD	Females****	SD
t_{max}	0.083	*	0.083	*	0.083 to 1	*	0.083 to 1	*	0.083 to 1	*	0.083 to 1	*
C_{max}	264.2	34.0	183.6	27.2	686.3	20.7	637.7	115.8	2417.4	306.2	1835.1	364.4
C_{max}/dose	26.4	3.4	18.4	2.7	22.9	0.7	21.3	3.9	24.2	3.1	18.4	3.6
AUC(0.083-96h)	9412	272	6845	814	26519	1785	24599	4688	89116	9816	83413	16326
AUC(0.083-96h)/dose	941	27	685	81	884	59	820	156	891	98	834	163
AUC(0.083-24h)	3566	348	2597	359	10107	253	9857	2148	34644	4243	31039	5469
AUC(0.083-24h)/dose	357	35	260	36	337	8	329	72	346	42	310	55

Some values were rounded

Units: t_{max} [h]. C [µg/mL]. Cmax/dose [(µg/mL)/(mg/kg)].

AUC [h·µg/mL]. AUC/dose [(h·µg/mL)/(mg/kg)].

*: not available or applicable.

**: n=3, results from one animal were not included due to an atypical profile

***: n=4

****: n=6

Table 2-2 Mean toxicokinetic parameters of ACZ885 in serum of marmosets in Week 11 of administration

	10 mg/kg				30 mg/kg				100 mg/kg			
Administration Week 11	Males**	SD	Females**	SD	Males**	SD	Females**	SD	Males***	SD	Females***	SD
t_{max}	0.083 to 1	*	0.083 to 1	*	0.083 to 1	*	0.083 to 1	*	0.083 to 8	*	0.083 to 1	*
C_{max}	469.8	107.6	375.8	53.8	1387.1	236.9	1240.5	113.7	3900.3	643.6	3646.7	739.1
C_{max}/dose	47.0	10.8	37.6	5.4	46.2	7.9	41.3	3.8	39.0	6.4	36.5	7.4
AUC(0.083-96h)	25768	5906	16823	1885	72741	19597	55132	6882	208838	49548	163321	30113
AUC(0.083-96h)/dose	2577	591	1682	189	2425	653	1838	229	2088	495	1633	301
AUC(0.083-24h)	8065	1352	6120	762	24474	5064	20077	2219	70689	14744	58475	9836
AUC(0.083-24h)/dose	806	135	612	76	816	169	669	74	707	147	585	98

Some values were rounded

Units: t_{max} [h]. C [µg/mL]. Cmax/dose [(µg/mL)/(mg/kg)].

AUC [h·µg/mL]. AUC/dose [(h·µg/mL)/(mg/kg)].

*: not available or applicable.

**: n=4

***: n=6

Table 2-3 **Mean toxicokinetic parameters of ACZ885 in serum of marmosets in Week 23 of administration**

	10 mg/kg				30 mg/kg				100 mg/kg			
Administration Week 23	Males**	SD	Females**	SD	Males**	SD	Females**	SD	Males***	SD	Females***	SD
t_{max}	0.083	*	0.083 to 1	*	0.083	*	0.083 to 24	*	0.083 to 1	*	0.083 to 1	*
C_{max}	738.1	178.0	536.0	55.5	2102.2	267.2	1635.7	573.9	5740.9	1397.5	4957.4	564.3
C_{max}/dose	73.8	17.8	53.6	5.6	70.1	8.9	54.5	19.1	57.4	14.0	49.6	5.6
AUC(0.083-96h)	36900	7818	23682	3859	95486	18644	78822	19174	268334	49763	226800	16925
AUC(0.083-96h)/dose	3690	782	2368	386	3183	621	2627	639	2683	498	2268	169
AUC(0.083-24h)	11630	1911	8393	1379	31587	5226	25562	6426	92493	13875	81484	9878
AUC(0.083-24h)/dose	1163	191	839	138	1053	174	852	214	925	137	815	99

Some values were rounded

Units: t_{max} [h]. C [µg/mL]. Cmax/dose [(µg/mL)/(mg/kg)].

AUC [h·µg/mL]. AUC/dose [(h·µg/mL)/(mg/kg)].

*: not available or applicable.

**: n=4

***: n=6

Study title: ***Subcutaneous Tolerability Study in Female Marmosets with Toxicokinetics***

Key study findings:

- Findings possibly secondary to potential ACZ885-related immunosuppressive effects:
  - Jejunum: slight hyperplasia (epithelial and Peyer's patch) with marked lymphocytic infiltrate and minimal abscess 1/4 HDF
  - Gall Bladder: slight leukocytic infiltrate in 1/4 MDF and 1/4 HDF
- Additional findings with unlikely relationship to treatment:
  - Liver: slight (1 HDF) and minimal-moderate (1/2 control F, 3/4 LDF, 2/4 MDF, 3/4 HDF) hepatocellular vacuolation; note 50% incidence in the contols
  - Anemia on Day 44 with ↓RBC, Hgb, and HCT, and inflammatory leukocytosis with ↑lymphocytes, monocytes, and eosinophils; note, observed in 1 of 4 mid-dose males, only
- NOAEL for direct treatment-related toxicity = 150 mg/kg/twice. 43 days apart by SC injection, based on low incidence of findings, that are considered to be secondary to possible immune response; findings related to slight increase in incidence of infection are monitorable

Study no.: 0370163
Conducting laboratory and location: Novartis Pharmaceutical Corporation, East Hanover, New Jersey
Date of study initiation: October 13, 2003
GLP compliance: Yes
QA report: yes (x) no ( )
Drug ACZ885, **lot #** (Batch) 4793, **and % purity**: 100.2%

Methods

Doses: 0 (vehicle control), 5 (LD), 50 (MD), and 150 (HD) mg/kg, based on results of 4-week IV toxicity study #0280160
Species/strain: Female Marmoset monkey (*Callithrix jacchus*)
Number/sex/group or time point (main study): 2 control F, 4F/dose group; Animal allocation is presented below (reproduced from the original BLA submission):

Table 3-1 Study design, animal allocation and test article doses

Group	Number	Animal Numbers	Dose (mg/kg)	Concentration (mg/mL)
1 Control	2	1501-1502	0	0
2 Low	4	2501-2504	5	5
3 Mid	4	3501-3504	50	50
4 High	4	4501-4504	150	150

Route, formulation, volume, and infusion rate: Test article (150 mg/ml in sterile water for injection, USP) diluted in vehicle containing 92.43 mg/ml sucrose, 4.65 mg/ml L-histidine, and 80:0.60 Tween (qs with purified water, USP), administered by subcutaneous (SC) injection on posterior region of the back, each injection on alternate (right or left) sides, on Days 1 and 43 at 0, 5, 50, or 150 mg/ml, 1 ml/kg
Satellite groups used for toxicokinetics or recovery: No recovery animals, as this study was exploratory, intended for dose-selection
Age: 2-5 years
Weight: 386.5-534.3 g
Additional study design or methodology: Animals pair-housed in modified stainless steel cages, 71-79 degF room temperature, 35%-85% humidity, 12-hour light/dark cycle; food (Uncertified Mazuri Callitrichid Diet #5MI5, acacia gum, egg whites, rice, fruits, vegetables) provided twice daily with fruit treat after dosing; tap water provided *ad libitum*; environment enriched with toys, wood sticks, nesting and enrichment boxes, seeds, Betta chips, Aspen shavings, nylon bone with holes, radio, TV

Observations and times:
Mortality: Twice daily (AM, PM)
Clinical signs: Once daily at baseline, twice daily (pre-dose, 2h after dosing) on Days 1 and 43, daily on all other days, with additional inspection of injection site for 3 days after dosing
Body weights: Baseline, on Treatment Days 1 & 43, and on Study Days 8, 15, 22, 29, 36, and 44
Food consumption: Daily throughout 43-day Treatment phase
Ophthalmoscopy: Not conducted

EKG: Not conducted

Hematology:

- Blood samples (0.5 ml) from all animals at pre-dose, and on Days 40 and 44 (before necropsy)
- Standard parameters assessed (including erythrocytes, hematocrit, hemoglobin, Wintrobe indices, red cell distribution width (RDW), reticulocytes, white blood cell count, white blood cell differential, and platelets

Clinical chemistry:

- Blood samples (0.5 ml) from all animals at pre-dose, and on Days 40 and 44 (before necropsy)
- Standard parameters assessed (including alanine aminotransferase, albumin, A/G ratio, alkaline phosphatase, aspartate aminotransferase, blood urea nitrogen, calcium, chloride, creatinine, globulin, glucose, inorganic phosphorus, potassium, protein electrophoresis, sodium, total bilirubin, total cholesterol, triglycerides, and urea)

Urinalysis: Not conducted

Gross pathology: All animals at necropsy on Day 44

Organ weights:

- All animals at necropsy on Day 44
- Organs weighed: heart, kidneys, brain, liver, spinal cord

Histopathology: Adequate Battery: yes (x)*, no ( ) *for the exploratory study
Peer review: yes (x), no ( )

- Organ and tissue samples examined (including aorta, application/injection site, bone marrow smear, brain, cecum, cervix, colon, duodenum, esophagus, eyes, adrenals, femur, gall bladder, gross lesions, heart, ileum, jejunum, kidneys, lacrimal gland, liver, lungs, mammary glands, lymph nodes (axillary, bronchial, inguinal, macroscopic lesions, mandibular, mesenteric), ovaries, pancreas, parathyroids, pituitary, rectum, salivary glands, sciatic nerve, skeletal muscle, skin/animal identification, spinal cord, spleen, sternum, stomach, thymus, thyroid, tongue, trachea, urinary bladder, uterus, and vagina)
- No examination of epididymides, parotids, prostate, seminal vesicles, and testes

Toxicokinetics: Blood samples (0.5 ml) from all animals at baseline and at 0.083, 24, 48, 72, 96, 120, 192, 264, 336, 504, 672, 936, and 1008 hours after the first (Day1) dose

Other:

Anti-ACZ885 antibody analyses:

- Blood samples (0.5 ml) collected at baseline and before the 2nd dose on Day 43, from all animals
- Samples processed using Biosensor — b(4)

Results

Mortality: No deaths occurred

Clinical signs: No treatment-related effects

Body weights: No treatment-related effects

Food consumption: No treatment-related effects

Hematology: No treatment-related effects; one MD animal showed anemia on Day 44 with ↓RBC, Hgb, and HCT, and inflammatory leukocytosis with ↑lymphocytes, monocytes, and eosinophils, not considered to be treatment-related due to absence of findings at the HD

Clinical chemistry: No treatment-related effects

Gross pathology: No treatment-related effects; occasional subcutaneous discoloration at injection site in all groups including controls

Organ weights: No treatment-related effects

Histopathology:

- Jejunum: slight hyperplasia (epithelial and Peyer's patch) with marked lymphocytic infiltrate and minimal abscess in 1/4 HDF
- Gall Bladder: slight leukocytic infiltrate in 1/4 MDF and 1/4 HDF
- Liver: slight (1/4 HDF) and minimal-moderate (1/2 control F, 3/4 LDF, 2/4 MDF, 3/4 HDF) hepatocellular vacuolation, unlikely to be treatment-related due to 50% incidence in the controls
- Extramedullary hematopoiesis in several organs, nephropathy (basophilic tubules, syncytia, tubular pigment), and hepatic vacuolation; thyroid follicular adenoma in 1/2 control F, and metastatic adenocarcinoma in axillary and inguinal lymph nodes in 1/4 LDF: Observations within background incidence and/or with no relationship to test article or dose

Toxicokinetics:

- Tmax 24-120 hours
- Less than dose-proportional increase in exposure ($AUC_{0\text{-}1008h}$) from 5-150 mg/kg, although Cmax appeared dose-proportional from 5-50 mg/kg but not from 50-150 mg/kg
- Half-life (672-1008h) = 108, 131, and 135 hours at 5, 50 and 150 mg/kg, respectively (4.5, 5.5, and 5.6 days, respectively)
- The results of the TK analyses are presented in the following table (from the original BLA submission):

Table 4-1 Mean toxicokinetic parameters of ACZ885 in marmoset serum

	5 mg/kg		50 mg/kg		150 mg/kg	
	Females	SD	Females	SD	Females	SD
t_{max}	24 to 120	n. a.	24 to 72	n. a.	24 to 72	n. a.
C_{max}	33.07	7.16	307.86	85.31	488.34	165.55
C_{max}/dose	6.61	1.43	6.16	1.71	3.26	1.10
AUC(0-1008h)	8120	3396	59772	22091	97684	37847
AUC(0-1008h)/dose	1624	679	1195	442	651	252
$t_{1/2}$(672 to 1008h)	108	4	131	14	135.3	56.4

Units: t [h]. C [µg/mL]. C/dose [(µg/mL)/(mg/kg)]. AUC [h·µg/mL]. AUC/dose [(h·µg/mL)/(mg/kg)].
n. a.: not applicable

Anti-ACZ885 antibody analyses: No evidence found for anti-ACZ885 antibody formation

Study title: ***13-Week Subcutaneous Toxicity Study in Marmosets with an 8-Week Recovery Period***

Key study findings:

- No treatment-related effects by SC ACZ885 in Marmosets administered doses from 15-150 mg/kg/twice weekly for 13 weeks and after 8 week recovery period on standard toxicology parameters
- Dose-related increase in minimal lymphoid hyperplasia of spleen (large active follicles) in the Treatment and Recovery males not considered to be treatment related for the following reasons:
  - Observed in absence of treatment-related effects on phenotyping of splenic suspensions and blood samples
  - Observed in the absence of anti-drug antibody formation
  - Observed in the absence of corresponding treatment-related changes in hematology parameters and/or spleen weights
  - No findings in spleen in the females in this study
  - Not replicated by conclusive findings in the other nonclinical toxicology studies, including the 6-month IV toxicology evaluation in marmosets
  - Patients monitored in clinical treatment showed no increases in spleen size
- No treatment-related effects on serum testosterone levels and immunophenotyping as evaluated in peripheral blood leukocytes and splenic suspensions
- NOAEL = 150 mg/kg/twice weekly SC for 13 weeks (with the exception of splenic hyperplasia not observed in the female marmosets in this study and not found in the other toxicology studies including the 6-month IV toxicity study in marmosets, and the reproductive and juvenile toxicity and immunotoxicity studies in mice

Study no.: Novartis Study 0470033

Conducting laboratory and location: Novartis Pharmaceuticals Corporation, East Hanover, New Jersey
Date of study initiation: March 8, 2004
GLP compliance: Yes
QA report: yes (x) no ( )
Drug ACZ885, **lot #** (Batch) 031205), **and % purity:** 101%

Methods

Doses: 0 (vehicle control), 15 (LD), 50 (MD), and 150 (HD) mg/kg, based on the results of the 43-day preliminary tolerability study in Marmosets (Study 0370163) showing no direct or serious treatment-related effects at SC doses of up to 150 mg/kg
Species/strain: Marmoset monkey (*Callithrix jacchus*)
Number/sex/group or time point (main study): 4/sex/dose group
Animal allocation is provided in the following table (from the original BLA submission):

Table 3-1 Study design, animal allocation and test article doses

		Animal Numbers		Dose	Concentration
Group	Number/sex	Males	females	(mg/kg)	(mg/mL)
1	4	1001-4	1501-4	0	0
Control	+2 recovery	1005-6	1505-6		
2	4	2001-4	2501-4	15	50
Low					
3	4	3001-4	3501-4	50	50
Mid					
4	4	4001-4	4501-4	150	50
High	+2 recovery	4005-6	4505-6		

Route, formulation, volume, and infusion rate: ACZ885 in placebo vehicle (30 mM L-histidine, 9.2% (m/V, 270 mM) D-sucrose, and 0.06% (m/V) Polysorbate 80), administered by subcutaneous (SC) injection in posterior region of the back, alternating right and left sides, at 0.3, 1, and 3 ml/kg at the LD, MD and HD, respectively, and 3 ml/kg in the placebo control vehicle group, twice weekly for 13 consecutive weeks (Mondays and Thursdays)
Satellite groups used for toxicokinetics or recovery: 2/sex control and HD for 8-week reversibility phase
Age: 2-6 years
Weight: 340.1-448.7 g males, 340.0-449.6 females
Additional or Unique methodology:

- Animals pair-housed in temperature controlled (76-84 degF) and humidity controlled (30%-80%) animal rooms with 12-hour light/dark cycle
- Provided Uncertified Mazuri Callitrichid Diet #5MI5 and New World Primate Diet #5040, with additional acacia gum, egg whites, rice, fruits and vegetables; water provided *ad libitum*
- Anti-ACZ885 antibody analyses not conducted under GLP

Observations and times:
Mortality: Twice daily on weekdays, once daily on weekends/holidays
Clinical signs: Once daily during baseline, twice daily (before and 2 hours after dosing) during the Treatment phase, including injection site (3 days after dosing)
Body weights: Once weekly during baseline, Treatment, and Recovery phases
Food consumption: Daily, individual values estimated due to pair-housing of animals throughout Treatment and Recovery phases
Ophthalmoscopy: All animals, at baseline and in the controls and HD animals during Week 12
EKG: All animals at baseline and during Treatment Week 13
Hematology:

- Blood samples (0.5 ml) collected from all animals at baseline and during Treatment week 13 and Recovery Week 8
- Parameters evaluated: erythrocytes, hematocrit, hemoglobin, Wintrobe indices, red cell distribution width (RDW), reticulocytes, white blood cell count, white blood cell differential, and platelets

Serum Testosterone:

- Blood samples collected from all animals at baseline, during Treatment Week 13, and Recovery Week 8
- 150 µl serum/animal frozen and stored for analysis

Immunophenotyping:

- Blood samples (0.6 ml) collected from all animals at baseline and during Treatment Week 13 and Recovery Week 8
- Parameters evaluated: peripheral blood leukocytes: CD20, CD3, CD4, CD8, CD16, CD4:CD8, CD3:CD20; Splenic nucleated cell suspension: CD20, CD3, CD4, CD8, CD4:CD8, CD3:CD20

Clinical chemistry:

- Blood samples (1 ml) collected from all animals at baseline and during Treatment Week 13 and Recovery Week 8
- Parameters evaluated: alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, total bilirubin, total protein, albumin (A), globulins (G), glucose, urea, creatinine, sodium, potassium, chloride, calcium, inorganic phosphorus, triglycerides, cholesterol, A/G ratio

Urinalysis: Not conducted
Gross pathology: All animals at necropsy at the end of Treatment and Recovery phases
Organ weights: All animals at end of Treatment and Recovery phases; organs (paired organs weighed separately) weighed included adrenals, brain, heart, kidneys, liver, ovaries, pituitary, prostate, spleen, testes, thyroid, and uterus
Histopathology: Adequate Battery: yes (x), no ( )
Peer review: yes (x), no ( )
Organs and tissues examined: adrenals, aorta, bone marrow (in bone and smear), brain, cecum, cervix, colon, duodenum, epididymis, esophagus, eye, femur (distal with joint), gall bladder heart, ileum, jejunum, kidney, lacrimal gland, liver lung, lymph nodes (axial, bronchial, inguinal, mandibular, mesenteric), mammary glands, ovaries, pancreas, parathyroid, pituitary, prostate, rectum, salivary gland, sciatic nerve, seminal vesicle,

skeletal muscle, skin, spinal cord, spleen, sternum, stomach, testes, thymus, thyroid, tongue, trachea, urinary bladder, uterus, vagina, macroscopic lesions, and injection sites; Additional sections collected from spleen for immunophenotyping at necropsy.
Anti-ACZ885 antibody determination: Blood samples (0.5 ml) collected at baseline and on th eday of necropsy from all animals
Gene expression analysis: Blood samples (1.2 ml) collected before necropsy from all animals at end of Treatment and Recovery phases; additionally, liver, kidney, spleen, lung, mesenteric lymph nodes and blood were sampled for gene expression analyses in a separate, exploratory investigation
Toxicokinetics: Blood (0.5 ml) was collected at baseline and on Study Days 1-3 (0.083, 12, 24, 48 hours after dosing, at pre-dose on Day 4 and on last Treatment Day (0.083, 12, and 24 hours after dosing); Recovery animals sampled at pre-dose (last dose), and 0.083, 12, 24, 48, 72, 120, 264, and 504 hours after the last dose and prior to necropsy at end of Recovery phase

Results

Mortality: No deaths observed during the study

Clinical signs: No treatment-related effects during Treatment and Recovery periods; injection site redness, bruising, scabbing, and changes in feces observed in all groups including controls

Body weights: No treatment-related effects during Treatment and Recovery periods

Food consumption: No treatment-related effects during Treatment and Recovery periods

Ophthalmoscopy: No treatment-related effects during Treatment and Recovery periods

EKG: No treatment-related effects during Treatment and Recovery periods

Hematology: No treatment-related effects during Treatment and Recovery periods

Immunophenotyping: No treatment-related effects observed in the blood samples and spleen cellular suspensions during Treatment and Recovery periods

Clinical chemistry: No treatment-related effects during Treatment and Recovery periods

Hormone analysis: No treatment-related effects on testosterone concentrations during Treatment and Recovery periods

Gross pathology: No treatment-related effects during Treatment and Recovery periods

Organ weights: No treatment-related effects during Treatment and Recovery periods

Histopathology:

- **Dose-related increase in minimal lymphoid hyperplasia of spleen** (large active follicles) in the Treatment and Recovery males, observed in absence of treatment-related effects on phenotyping of splenic suspensions and blood samples, anti-drug antibody levels, and treatment-related findings in the spleen in the female animals
- The results of the histopathology examination of spleen at the end of the Treatment period are presented in the following table (from the original BLA submission):

		INCIDENCE OF MICROSCOPIC FINDINGS							
		Males				Females			
ORGAN/TISSUE	TREATMENT	0 mg/kg/day	15 mg/kg/day	50 mg/kg/day	150 mg/kg/day	0 mg/kg/day	15 mg/kg/day	50 mg/kg/day	150 mg/kg/day
SPLEEN		(4)	(4)	(4)	(4)	(4)	(4)	(4)	(4)
Within normal limits		3	2	2	1	4	3	1	3
Depletion, lymphoid.									
minimal		1	1				1	1	
Depletion, lymphoid.									
Score Expanded Totals		1	1				1	1	
Hyperplasia, lymphoid.									
minimal			1	2	2				
slight					1				
Score Expanded Totals			1	2	3				
Pigment, macrophage, focal.									
minimal			1						
Score Expanded Totals			1						
Extramedullary hematopoiesis, increased.									
minimal					2			1	1
slight		1					1	2	
Score Expanded Totals		1			2		1	3	1

Figures in ( ) represent the number of animals from which this organ/tissue was examined microscopically

- The results of the histopathology examination of spleen at the end of the Recovery period are presented in the following table (from the original BLA submission):

		INCIDENCE OF MICROSCOPIC FINDINGS			
		Males		Females	
ORGAN/TISSUE	TREATMENT	0 mg/kg/day	150 mg/kg/day	0 mg/kg/day	150 mg/kg/day
HEMOLYMPHATIC SYSTEM					
SPLEEN		(2)	(2)	(2)	(2)
Depletion, lymphoid.					
Score Expanded Totals					1
Hyperplasia, lymphoid.					
minimal			1		
Score Expanded Totals			1		
Hyperplasia, reticulum cell.					
minimal			1		
Score Expanded Totals			1		

- **Minimal leukocytic or mononuclear infiltrates at injection site,** without dose-relationship

Anti-ACZ885 antibody determination: No anti-ACZ885 antibodies detected at the end of the Treatment and Recovery phases

Toxicokinetics:

- Dose-proportional increase in exposure (AUC and Cmax) on Day 1-3 across doses, suggesting accumulation
- Increased exposure (2X-3X relative to Day 1 AUC and Cmax values) in Week 14, suggesting accumulation
- Tmax 12-96 hours on Day 1 and 0-24 hours in Week 14
- Apparent $t_{1/2}$ = 143 hours (6 days) in males and 127 hours (5.3 days) in females
- No gender differences in TK paramters

Table 2-1 Mean toxicokinetic parameters of ACZ885 in serum of marmosets on day 1-3 of administration

	15 mg/kg				50 mg/kg				150 mg/kg			
Administration Day 1	Males*	SD	Female*	SD	Males*	SD	Female*	SD	Males*	SD	Female*	SD
t_{max}	12 to 24	**	24 to 96	**	12 to 96	**	12 to 48	**	24 to 96	**	48 to 96	**
C_{max}	112.5	19.9	88.9	18.2	401.1	48.8	366.7	30.4	990.2	116.6	926.7	230.0
C_{max}/dose	7.5	1.3	5.9	1.2	8.0	1.0	7.1	0.4	6.6	0.8	6.2	1.5
AUC(0-96h)	9344	1348	8890	1053	31726	5118	25923	2153	79391	8951	75422	17299
AUC(0-96h)/dose	556	90	459	70	638	102	536	43	511	60	503	115
AUC(0-24h)	1873	436	1485	379	5344	799	5497	997	13197	1743	14206	3464
AUC(0-24h)/dose	125	29	99	25	127	15	110	18	88	12	95	23

Units: t_{max} [h], C [µg/mL], Cmax/dose [(µg/mL)/(mg/kg)],
AUC [h·µg/mL], AUC/dose [(h·µg/mL)/(mg/kg)].
*: n=6
**: not applicable

Table 2-2 Mean toxicokinetic parameters of ACZ885 in serum of marmosets on week 14 of administration

	15 mg/kg				50 mg/kg				150 mg/kg			
Administration Week 14	Males*	SD	Female*	SD	Males*	SD	Female*	SD	Males**	SD	Female**	SD
t_{max}	12 to 24	****	12 to 24	****	12 to 24	****	12	****	0 to 24	****	0.083 to 24	****
C_{max}	342.0	112.1	241.6	35.0	1170.3	381.8	1001.3	318.7	2210.1	257.1	2336.2	562.2
C_{max}/dose	22.8	7.5	16.1	2.4	23.4	7.6	20.0	6.4	14.7	1.7	15.6	3.7
AUC(0-1368h)***	****	****	****	****	****	****	****	****	482113	7859	342749	142562
AUC(0-1368h)/dose***	****	****	****	****	****	****	****	****	3081	51	2285	953
AUC(0-24h)	7144	2574	5151	891	24673	7350	20920	5218	48954	5933	50170	10867
AUC(0-24h)/dose	475	172	343	59	493	147	419	104	313	46	334	72
$t_{1/2}$(504-1368h) ***									143	15	127	9

Units: t_{max} [h], C [µg/mL], Cmax/dose [(µg/mL)/(mg/kg)],
AUC [h·µg/mL], AUC/dose [(h·µg/mL)/(mg/kg)].
*: n=6
**: n=3, main study and recovery animals
***: n=2, only recovery animals
****: not applicable or available

Study title: ***13-Week, Twice Weekly Subcutaneous Batch Comparison Study in Marmosets***

Purpose:

- To compare TK and toxicity profiles of ACZ885 lyophilisates at 150 mg/kg produced by two different processes:
  - Formulation A (also called Process B; produced in ——
    - Note: This is considered more representative of the final process
  - Formulation B (also called Process A; produced in ——

b(4)

- Note: Formulation B represents the prior formulated product evaluated in all other toxicity studies

Key study findings:

- **Deaths in 2 M cagemates** (#3004 euthanized on Day 57, #3003 found dead on Day 72) given ACZ885 lyophilisates from —— (Formulation B) at 150 mg/kg/twice weekly, showing signs of septicemia in one M and lymphoid depletion in the other M b(4)
- **Fecal changes** in 3/4-4/4 M given Formulation B —— and 2/4-3/4 F given Formulation A —— , diarrhea and/or mucoid) b(4)
- **Body weight loss** higher in animals administered Formulation B —— , vs. controls and vs. Formulation A ——) groups
- Mild-moderate **decreased serum albumin** in 3/4 M and 1/4 F given Formulation B ——
- **NOAEL for the to-be-marketed Formulation A** (ACZ885 made from —— —— **= 150 mg/kg/twice weekly** for 13 weeks b(4)
- **NOAEL for Formulation B** used in the nonclinical toxicology studies and early clinical trials (ACZ885 lysophilisates made from —— used in previous toxicology studies) **not determined**

Study no.: Novartis Study # 0770370
Conducting laboratory and location: Novartis Pharmaceuticals Corporation, East Hanover, New Jersey
Date of study initiation: October 9, 2007
GLP compliance: Yes (except for anti-ACZ885 antibody determination and lymphocyte immunophenotyping)
QA report: yes (x) no ( )
Drug ACZ885 150 mg liquid in pre-filled syringe 1 ml, derived from —— (Formulation A), **lot #** (Batches) 9502.01.A and 077201, **and % purity**: 99.5% (9502.01) b(4)
Drug ACZ885 lyophilisates from —— (Formulation B), **lot #** (Batch) Y0060106, **and % purity**: 99.37%

Methods

Doses: 0 (Sterile Water for Injection vehicle control), 150 mg/kg/twice weekly ACZ885 from the —— (Formulation A) or 150 mg/kg/twice weekly ACZ885 lyophilisates from the —— (Formulation B), doses based on results of 13-week SC toxicity study (#0470033) in marmosets using ACZ885 derived from the —— b(4)
Species/strain: Marmoset monkey (*Callithrix jacchus*)
Number/sex/group or time point (main study): 4/sex/group
The animal allocations are presented in the following table (from the original BLA submission):

Group	Number/sex	Animal Numbers		Dose*	Concentration
		males	females	(mg/kg/day)	(mg/mL)
1 Control	4	1001-4	1501-4	0	0
2 ACZ885 Formulation A	4	2001-4	2501-4	150	150
3 ACZ885 Formulation B	4	3001-4	3501-4	150	150

*Doses were not corrected for active moiety.

Route, formulation, volume, and infusion rate: Formulation A provided in 150 mg/ml pre-filled syringes, Formulation B reconstituted using 1.0 ml Sterile Water for Injection, USP; administered by subcutaneous (SC) injection on alternating sides of back, twice weekly for 13 consecutive weeks
Satellite groups used for toxicokinetics or recovery: No satellite animals used; no recovery period evaluation, TK analyses performed on all main study animals
Age: >2 years
Weight: 335.1-451.4 g males and 303.1-509.6 g females
Additional study methodology:

- Animals pair-housed in temperature (76-84 degF) and humidity (40%-80%) controlled animal rooms, with 12-hour light/dark cycle
- Provided Purina New World Primate biscuits # 5040 in honey water, sweet potato, macaroni, eggs, whole wheat bagels, fruits and vegetables, and occasional treats of marshmallows and cereal; water provided *ad libitum*
- Enriched environment provided with toys, wood sticks, perches, nesting boxes with music and/or bed-o-cobs
- Anti-ACZ885 antibody analyses not conducted under GLP due to lack of available validated assay

Observations and times:
Mortality: Twice daily on weekdays, once daily on weekends and holidays
Clinical signs: Once daily during baseline, twice daily on dosing days (before and 2 hours after dosing) and once daily on non-dosing days during Treatment period
Body weights: Baseline and twice daily during Treatment Weeks 1 and 2, once daily during Treatment Weeks 3-13
Food consumption: Twice weekly in Treatment Weeks 1 and 2, weekly during Treatment Weeks 3-13
Ophthalmoscopy: Baseline and daily, estimated for individual animals due to pair-housing arrangement
EKG: Not done
Hematology:

- Venous blood (0.5 ml) collected from left leg at Baseline and during Treatment Weeks 5 and 12
  - Parameters evaluated: erythrocytes, hematocrit, hemoglobin, Wintrobe indices, red cell distribution width (RDW), reticulocytes, white blood cell

count, white blood cell differential, platelets, prothrombin (PT), activated partial thromboplastin time (aPTT), and fibrinogen

Clinical chemistry:

- Venous blood (1.0 ml) collected from left leg at Baseline and during Treatment Weeks 5 and 12
- Parameters evaluated: alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, total bilirubin, total protein, albumin (A), creatine kinase, globulins (G), glucose, urea, creatinine, sodium, potassium, chloride, calcium, inorganic phorphorus, triglycerides, cholesterol, and A/G ratio

Coagulation:

- Venous blood (0.9 ml) collected from left leg at Baseline and during Treatment Weeks 5 and 12

Urinalysis: Not done

Gross pathology:

- All animals, at end of the 13-week Treatment period

Organ weights:

- All animals, at end of 13-week Treatment period
- Organs weighed (paired organs weighed separately); adrenals, brain, heart, kidneys, liver, ovaries, pituitary, prostate, spleen, testes, thyroid, and uterus

Histopathology: Adequate Battery: yes (x), no ( )
Peer review: yes (x), no ( )

- All animals at the end of the 13-week Treatment period
- Organs and tissues examined: adrenals, aorta, bone marrow (in bone), brain, cecum, cervix, colon, duodenum, epididymis, esophagus, eye, femur (distal with joint), gall bladder, heart, ileum, jejunum, kidneys, lacrimal glands, larynx-cross section, liver, lungs, lymph nodes (bronchial, mandibular, mesenteric), mammary glands, injection sites, ovaries, oviducts, pancreas, parathyroids, pituitary, prostate, rectum, salivary glands, sciatic nerve, seminal vesicles, skeletal muscle (right leg), skin, spinal cord, spleen, sternum, stomach, testes, thymus, thyroid, tongue, trachea, ureter-cross section, urinary bladder, uterus, vagina, and macroscopic lesions

Toxicokinetics: Blood samples (0.5 ml) from all animals at baseline and on Treatment Days 1-3 and 4, at 7, 24, and 48 hours after dosing, and in Week 13 at 7, 24, 48, and 72 hours after dosing

Other: Anti-ACZ885 antibody determination: Blood samples (0.5 ml) from all animals in Treatment Week 13

Results

Mortality: Deaths in 2 M given Formulation B at 150 mg/kg/twice weekly

- Male #3004 euthanized on Day 57
  - **Clinical chemistry changes** (increased serum urea, creatinine, and phosphorus concentration, mild-moderate increased glucose, cholesterol, and triglycerides, and decreased sodium, potassium and chloride concentrations)
  - Necroscopy findings: **enlarged testes** (without histopathology correlates),

- Histopathology findings: **mixed inflammatory cell infiltration** in intestinal mucosa, **intestinal mucosal ulceration** w/ neutrophil loss and blood in lumen, **neutrophilic inflammation** with bacteria throughout body
- Death attributed to septicemia, secondary to intestinal ulceration
- Questionable relationship to treatment, in agreement with the Applicant, because similar finding in a Control F and common finding in marmosets

- M #3003 (cagemate of euthanized M) found dead on Day 72
  - **Marked thymus lymphoid depletion**
  - Cause of death not determined, possibly treatment-related

Clinical signs:

- Fecal changes in M given 150 mg/kg Formulation B: 75%-100% incidence of diarrhea, mucoid feces
- Fecal changes in F given 150 mg/kg Formulation A: 50%-75% incidence diarrhea
- No other treatment-related clinical signs observed

Body weights:

- All animals, including controls showed **body weight loss** (BWL) during the study, although BWL higher on Day 91 in M given 150 mg/kg Formulation B than in controls and 150 mg/kg Formulation A treated animals

Food consumption: No treatment-related effects

Ophthalmoscopy: No treatment-related effects

Hematology: No treatment-related effects

Coagulation: No treatment-related effects

Clinical chemistry:

- Mild-moderate **decreased serum albumin** in 3/4 M given 150 mg/kg Formulation B on Days 35 and 80 (animal #3001), baseline and Day 35 (animal # 3003) and Day 57 (animal #3004) , and in 1/4 F (#2502) also given 150 mg/kg Formulation B, at baseline and on Days 35 and 80, compared to baseline values (#3001 and #3004) and controls (all affected animals)
- Observations in the euthanized M on Day 57 (#3004): increased serum urea, creatinine, and phosphorus concentration, mild-moderate increased glucose, cholesterol, and triglycerides, and decreased sodium, potassium and chloride concentrations

Gross pathology: No treatment-related effects

Organ weights: No treatment-related effects