DEPARTMENT OF HEALTH AND HUMAN SERVICES
Office of Therapeutics Research and Review
Center for Biologics Evaluation and Research
Food and Drug Administration

MEMORANDUM

DATE: July 10, 1998

FROM: Barbara G. Matthews, M.D.
Medical Officer/Team Leader, Infectious Diseases and Immunology Branch, Division of Clinical Trial Design and Analysis (DCTDA)

SUBJECT: Review of BLA submission 98-0012

THROUGH: Karen Weiss, MD KW 7-31-98
Director of the Division of Clinical Trial Design and Analysis (DCTDA)

William Schwieterman, M.D., Branch Chief, Infectious Diseases and Immunology Branch, Division of Clinical Trial Design and Analysis (DCTDA) WJS 8/3/98

TO: File

PLA 98-0012

Sponsor: Centocor

Product: Chimeric (Human-Murine) Monoclonal Antibody (cA2) to Tumor Necrosis Factor for Inflammatory Bowel Disease (Infliximab, Remicade™)

Submission Date: 12-30-97

Clinical Reviewer: Barbara G. Matthews, M.D.

1.0 Overview of PLA 98-0012

1.1 Material Reviewed

135 volumes consisting of complete study reports and clinical data (including videoendoscopies and photographs) on 4 clinical trials in Crohn's disease patients. In addition the following study reports alone, i.e., no specific clinical data, were reviewed: 4 clinical trials evaluating cA2 for the treatment of ———————, one clinical trial in patients with ———————, one clinical trial in healthy volunteers and two clinical trials evaluating cA2 in ———

During the course of the review the sponsor submitted the following items for review:

1. March 11, 1998. Explanation for patient discontinuations during the ——————— phase of T16.

2. March 27, 1998. Analysis of infusion reactions and possible relationship to levels of bovine IgG in lots used in the clinical studies.

3. April 16, 1998. Updated safety review for 3 year follow-up as of March, 1998 of patients treated with cA2 in clinical trials.

4. May 20, 1998. Response to question regarding assessment of rectovaginal fistula in T20.

5. June 19 ,1998. Additional analyses of serum samples for autoantibodies.

1.2 Proposed Use

The proposed label described the following indications and usage:

> Infliximab is indicated for the treatment of patients with Crohn's disease to:
> - reduce signs and symptoms in patients with moderate to severe disease activity in whom conventional therapies are inadequate
> - close enterocutaneous fistula.

The proposed label described the following dosage and administration:

> The recommended dose for reducing signs and symptoms of moderate to severe disease activity is 5 mg/kg. In patients responding to an initial infusion of Infliximab, up to 4 infusions given at 8-week intervals may be administered to sustain clinical benefit.
>
> The recommended dose for closure of enterocutaneous fistulae is also 5 mg/kg; 2 additional 5 mg/kg doses should be administered at 2 and 6 weeks following the first infusion.

1.3 General Background

Pathogenesis. Crohn's disease most likely represents a heterogeneous group of disorders. After much effort that has focused on the identification of a specific pathogenic cause, it is being recognized that disease manifestations could result from a combination of any, or all of, a number of factors. At present, patients with Crohn's disease are grouped into homogeneous populations based on subclinical markers, genetic associations and clinical phenotypes. For example, absence of perinuclear antineutrophil cytoplasmic antibodies (pANCA) in the serum defines one population, while a smaller number of patients with pANCA represents another. Another serum marker, antierythrocyte autoantibody derived from the VH3-15 gene is markedly elevated in Crohn's disease patients but at lower levels in ulcerative colitis patients.

Genetic analyses define additional subpopulations and genetic associations of Crohn's disease. For example HLA class II DR or DQ alleles are associated with Crohn's disease. This association represents an independent risk factor and not a disequilibrium in linkage between the DR/DQ regions. A positive linkage of Crohn's disease to the HLA region was detected in Crohn's disease-only families. These findings support previously reported associations of Crohn's disease with the HLA class II genes and the TNF gene locus, all on chromosome 6.

The initial evidence that TNF-α plays a role in Crohn's disease was provided by the finding that high TNF-α levels can be detected in stool samples from Crohn's disease patients. Rodent models also provide strong evidence that dysregulation of T-helper 1

cells (Th1) plays a significant role in colitis. Upon normal activation, Th1 cells produce a wide range of cytokines including TNF-α, and IFN-γ. In a dysregulated state, these two cytokines are proinflammatory as evidenced by antibody blocking experiments. When administered to a T cell reconstituted SCID mouse model of colitis, anti-TNF-α and IFN-γ antibodies ameliorate the disease process. In humans, a genetic link of Crohn's disease to TNF has been established. A specific TNF microsatellite haplotype is associated with 25% of the Crohn's disease patients, defining a subset of patients with T cells that produce high levels of TNF in response to *in vitro* activation. Thus, strong clinical, animal, and genetic evidence exists that TNF-α plays a role in the inflammatory process seen in patients with Crohn's disease.

Clinical Presentation. Crohn's disease is a chronic inflammatory disease of the bowel characterized by segmental transmural inflammation and granulomatous changes. Although it affects primarily the distal small intestine and the colon, it may affect any part of the gut. Crohn's disease is more common in whites than blacks and Orientals, with an increased incidence (three- to six-fold) in the Jewish population compared to non-Jewish individuals. Both sexes are equally affected. In western Europe and the United States, Crohn's disease (colonic plus small bowel) has an incidence of approximately 2 cases per 100,000 population; the prevalence is estimated at 20 to 40 per 100,000 population. The incidence of Crohn's disease, particularly colonic disease, is believed to be increasing. Peak occurrence is between 15 and 35 years of age, although it is seen in every decade of life.

The clinical presentation of Crohn's disease will vary according to the anatomic location of the disease. The major clinical features include fever, abdominal pain, diarrhea and generalized fatigue. There may also be weight loss. Diarrhea and pain are most frequent with colonic involvement, which is also often accompanied by severe anorectal complications such as fistulas, fissures and perirectal abscesses. The extracolonic manifestation of arthritis is also commonly seen with colonic Crohn's disease.

Crohn's disease involving the small bowel typically has its onset in a young adult with a history of fatigue, variable weight loss, right lower quadrant discomfort or pain, and diarrhea. Low grade fever, anorexia, nausea and vomiting may also be present. The patient may also present with mild anemia, mild to moderate leukocytosis and an elevated erythrocyte sedimentation rate. The complications of the disease are often local and include intestinal obstruction, fistula formation, involvement of the stomach and duodenum, small-bowel and colonic malignancy, secondary amyloidosis, bile salt malabsorption and development of urinary oxalate stones.

Fistulae are a common complication of Crohn's disease, occurring in 15% to 32% of patients. Although fistulae rarely close spontaneously, they may improve with treatment of the underlying Crohn's disease.

The prognosis for Crohn's disease is generally unfavorable. In the majority of these patients, the course is chronic and intermittent regardless of the site of involvement. The disease responds less well to medical therapy with time, and over two-thirds of patients develop complications requiring surgery at some point. The mortality rate increases with the duration of disease and most likely ranges from 5% to 10%. Most deaths occur from peritonitis and sepsis. Following surgery, patients with Crohn's disease often have recurrence and relapses.

Measures of Disease Activity. Conventional laboratory testing provides only crude measures of disease activity. Upper endoscopy and colonoscopy are the most commonly used procedures to assess the extent and severity of colonic and upper gastrointestinal Crohn's disease. Features of active disease include discrete serpiginous ulcerations, skip areas, rectal sparing, strictures, and aphthoid ulcerations. Wall thickness, fistulae, and abscesses cannot be adequately assessed endoscopically.

While all segments of the gastrointestinal tract can be visualized radiographically, the small bowel examination is most useful since this region usually cannot be adequately viewed endoscopically. Detailed views of strictures, fistulae, sinus tracts, inflammatory masses, and ulceration are important features of small bowel radiography.

Pathologic review of biopsy or resected specimens often can aid in diagnosis and measurement of extent and severity of disease. Pathologically, Crohn's disease is described as a transmural disease with focal or microscopic skip areas of inflammation in the lamina propria. The degree of inflammation in the most heavily involved area often is an accurate assessment of the severity of disease. Demonstration of noncaseating granulomas with epithelial cells, macrophages, and multinucleated giant cells is inconsistent, but if multple sections are made, can be demonstrated in ~30% of resected Crohn's disease specimens.

Disease activity indices are used to objectively measure the activity of disease for judgment of response in clinical trials. The Crohn's disease activity index (CDAI) was developed during the 1979 National Cooperative Crohn's Disease Study to objectively assess response to therapy among patients studied at many participating centers. Although imperfect and cumbersome, e.g., requirement of recording of symptoms for 7 days and for hematocrits, the CDAI remains the most commonly index. Other indices include the Harvey & Bradshaw index, the Oxford index, the Van Hees index the Present score, the Index for Survey Research and the Sickness Impact Profile.

Biochemical markers of inflammation are numerous and useful only in limited settings, usually in clinical trials to assess activity of Crohn's disease. Such markers include acute-phase reactants (C-reactive protein), leukocyte related markers (lactoferrin), lysosomes, and cytokines (activated T-cells and IL-2 receptors).

Treatment of Crohn's disease. Because its cause is unknown, medical management of the disease is largely empirical and is designed to reduce inflammation. Therapies mainly consist of corticosteroids, antibiotics, aminosalicylates and immunomodulatory agents. Further details of each type of therapy, as abstracted from a review published by Hanauer (1996), are provided below.

- Corticosteroids, the first medications to be evaluated systematically in patients with inflammatory bowel disease, inhibit the production and action of cytokines and inflammatory mediators, enhance sodium and water absorption and improve the sense of well-being. Although corticosteroids are effective in patients with Crohn's disease, complications of treatment, including masking or induction of intestinal perforation, osteonecrosis, metabolic bone disease and growth retardation in children, can limit their use. These toxic effects of corticosteroids are related to the dose and duration of therapy. Since corticosteroid dependency is often seen in Crohn's disease patients and the dose cannot generally be tapered without an increase in disease activity, corticosteroid therapy is indicated primarily for the short-term induction of a remission of disease and not as a maintenance therapy.

- Among antibiotic therapies, metronidazole is effective in treating perianal disease and is as effective as sulfasalazine and superior to placebo as single therapy in patients with mildly to moderately active disease. Long-term therapy with metronidazole is required, since relapse is likely once treatment is stopped. However, extended therapy often carries the risk of peripheral neuropathy, especially when daily doses are in excess of 10 mg/kg. Despite empirical data on the use of other antibiotics in patients with Crohn's disease, no combination of antibiotics has been found to alter the long-term course of Crohn's disease.

- Among aminosalicylates, sulfasalazine and 5-aminosalicylic acid analogues are most commonly used to treat mildly or moderately active Crohn's disease and to maintain remission. Sulfasalazine is not as effective as corticosteroids for inducing remission in patients with moderate or severe disease. Common side effects of sulfasalazine include headache, nausea and fatigue; these effects respond to a reduction in dose. Hypersensitivity reactions to the sulfa moiety include rash, fever, hepatitis, pneumonitis, hemolytic anemia and bone marrow suppression. There is improved tolerance to the newer mesalamine derivatives.

- Immunomodulatory drugs, including azathioprine or mercaptopurine, cyclosporine and methotrexate, are accepted as appropriate for long-term treatment in some patients with Crohn's disease. The mechanism of action of these drugs may involve inhibition of lymphocyte function, primarily that of T cells. The addition of azathioprine or mercaptopurine to corticosteroids allows tapering of the latter in patients with Crohn's disease. A clinical response requires 3 to 6 months of therapy. Although generally well tolerated, azathioprine/mercaptopurine therapy results in pancreatitis in 3% to 15% of patients. Both agents also cause dose-related bone

marrow suppression. The slow onset of action of azathioprine and mercaptopurine is problematic and induced the development of more potent immunosuppressive drugs, such as cyclosporine, for which the primary use is refractory Crohn's disease. Although continuous infusions of cyclosporine have proven effective, lower-dose oral regimens have not been consistently effective in either inducing or maintaining remission. Renal dysfunction, manifested as a decrease in glomerular filtration, interstitial nephritis or both, is the primary side effect of cyclosporine. Other complications of therapy include neurotoxic effects and seizures, immunosuppression and opportunistic infections. As a result, cyclosporine is typically reserved for the treatment of severe refractory disease when surgery is inappropriate or before other therapies have taken effect. A final immunomodulatory agent, methotrexate, has demonstrated significant corticosteroid-sparing effects. However, the potential for bone marrow suppression and hepatic toxicity requires frequent monitoring of blood counts and liver enzyme concentrations.

Currently available medical therapies for patients with fistulizing Crohn's disease are associated with a relatively low response rate, prolonged onset of response or inability to maintain a therapeutic response unless given as a continuous infusion. For example:

- Treatment with 6-mercaptopurine resulted in closure in 13 of 34 (39%) of patients; however, the mean time to onset of response was 3.1 months.

- Intravenous cyclosporine administered continuously over approximately 1 week resulted in closure in 7 of 16 (44%) patients. However, closure was maintained in only 3 (21%) of the patients after switching to oral cyclosporine.

Chimeric (Human-Murine) Monoclonal Antibody (Infliximab, cA2). Chimeric A2 (cA2) is a recombinant human-murine chimeric IgG1, κ human-murine chimeric monoclonal antibody, that specifically binds both soluble TNFα homotrimer and the membrane-bound precursor form of TNFα. It was developed for therapeutic use in diseases such as Crohn's disease, where over-expression of TNFα is thought to be involved with the chronic inflammatory state. It has a high affinity for TNFα (Ka = 10^{10} M^{-1}) and probably functions by inhibiting or preventing interactions of over-expressed TNFα with its cellular receptors, p55 and p75. By blocking excessive TNF-mediated signaling through these two receptors, cA2 may prevent deleterious effects caused by dysregulated TNFα.

Results from preclinical studies indicated that cA2 effectively and potently binds TNFα and that cA2 blocks the typical disease progression seen in ———————. In addition to Crohn's disease, Centocor is actively investigating the safety and efficacy of cA2 for the treatment of ———————.

Description of the production of cA2. Infliximab (cA2) is manufactured at Centocor B.V. in Leiden, The Netherlands, and is formulated, filled into vials and lyophilized at

The antibody is produced by cultured cells transfected with a DNA expression construct containing murine immunoglobulin variable and human constant region genes. The antibody is isolated by a purification scheme that involves multiple chromatography and specific virus inactivation steps. Infliximab consists of 100 mg of the cA2 antibody lyophilized with sucrose, $NaPO_4$, and polysorbate 80. Each individual lot of Infliximab is tested for sterility, identity, purity and potency. Infliximab potency is measured as inhibition of TNF mediated cytotoxicity of cultured WEHI 164 fibrosarcoma cells. Centocor has demonstrated that they can manufacture sterile mAb with a defined charge and glycoform composition, undetectable or low levels of contaminants and aggregates, and consistent potency.

Mechanism of Action. cA2 clears pro-inflammatory TNF from the circulation and possibly deletes aberrantly activated mTNF expressing T cells. This mechanism of action is supported by several pre-clinical experiments.

nfliximab and complement lyse mTNF positive T cells. Finally, Infliximab down modulates inflammatory disease activity in a human TNF transgenic (Tg197) mouse.

Clinical Experience. Centocor has conducted clinical trials evaluating the use of cA2 in patients with Crohn's disease, The following list of clinical trials are completed.

- one phase I and three phase II clinical trials in (total n = 222). Centocor is actively developing cA2 for the treatment of and has an ongoing phase III clinical trial.

- s. a phase II clinical trial in 11 patients. No benefit was seen and there is no ongoing development for this indication.

- : a total of 113 patients with were enrolled in two phase 2 trials. No benefit was seen. There is no ongoing development of cA2 for this indication.

- Crohn's disease. Centocor conducted four clinical trials evaluating the safety and efficacy of cA2 for the treatment of Crohn's disease (Table 1).

Table 1. Clinical Trials evaluating cA2 as therapy in patients with Crohn's disease

Protocol (No. of Sites) (No. of Pts.)	Phase	Study Design	Dose Regimens	Number of Patients Treated	Total cA2 Treated Patients
T08 (sites = 1) (n = 10)	Phase I	Open-label	10 mg/kg x 1 20 mg/kg x 1	8 2	10
T11 (sites = 7) (n=21)	Phase II	Open-label	1 mg/kg x 1 5 mg/kg x 1 10 mg/kg x 1 20 mg/kg x 1	5 5 5 6	21
T16 (sites = 18) (n=108)	Phase II	Initial phase: Placebo controlled, double-blind	Placebo x 1 5 mg/kg x 1 10 mg/kg x 1 20 mg/kg x 1	25 27 28 28	108
		Open-label extension	10 mg/kg x 1	48	
T20 (sites = 12) (n=24)	Phase III	Placebo controlled, double-blind	Placebo x 3 5 mg/kg x 3 10 mg/kg x 3	31 31 32	63

T8

There were 9 evaluable patients in the open-label, phase I clinical trial T8 (one patient experienced a serious adverse event and did not have the last clinical evaluation). The eligibility criteria included a CDAI >150 one week prior to enrollment and that patients be unresponsive to corticosteroid therapy. Clinical remission (CDAI <150) was achieved in 89% of the patients from the 2-week evaluation visit through the last evaluation at week-8. The CDEIS score decreased in all evaluable patients at week 4.

T11

Twenty patients with CDAI scores ≥220 and <400 were considered evaluable in the phase II clinical trial T11. This trial was designed in two parts. A dose was to be selected from results of part 1 and used to evaluated safety and efficacy in part 2. Part 1 was completed and part 2 was replaced with clinical trial T16. 90% achieved the primary endpoint response of a 70 point reduction from baseline in CDAI score at any time during the 4 week evaluation period.

T16 and T20

Data from T16 are intended to support the indication of "reduction of signs and symptoms in patients with moderate-severe Crohn's disease." In addition, data from T20

are intended to support the indication of "closure of fistula." The clinical trials T16 and T20 are described in sections 2.0 and 3.0, respectively.

Of the 233 patients enrolled into these 4 trials, 177 received cA2. Except for a 14 year old patient treated with cA2 on a compassionate basis, all patients were >18 years of age.

1.4 Orientation to the Clinical Review

The clinical review will discuss the assessment of the clinical efficacy data for T16, the pivotal trial to support the use of cA2 for chronic treatment, and for T20, the pivotal trial to support the cA2 in the closure of fistulae. The review discusses the clinical indication as originally submitted

. An in-depth analysis of the clinical data generated from T8 and T11 are not be presented because they are small, open label, phase 1 studies that were not designed to support licensure. Endoscopies from the clinical trial T8 were reviewed as summarized in Dr. Brian Harvey's review.

Because of the small sample population studied in each of the clinical trials, the differences in drug exposure, and the small number of patients who were exposed to placebo only, the safety review will summarize the assessment of safety for cA2 administered to patients in completed clinical trials evaluating Crohn's and

2.0 Protocol T16 (C0168T16): A placebo-controlled, dose-ranging study followed by a placebo-controlled, repeated-dose extension of anti-TNF chimeric monoclonal antibody (cA2) in the treatment of patients with active Crohn's disease.

2.1. Study Proposal

2.1.1 Background

T16 was designed as a phase 2 clinical trial to determine an effective dose in the acute treatment of patient's with active Crohn's disease no responding to immunosuppressant therapy and to explore maintenance therapy with a single dose in patients who respond initially. This clinical trial became the pivotal trial in support for licensure of cA2 for this indication

2.1.2 Objectives

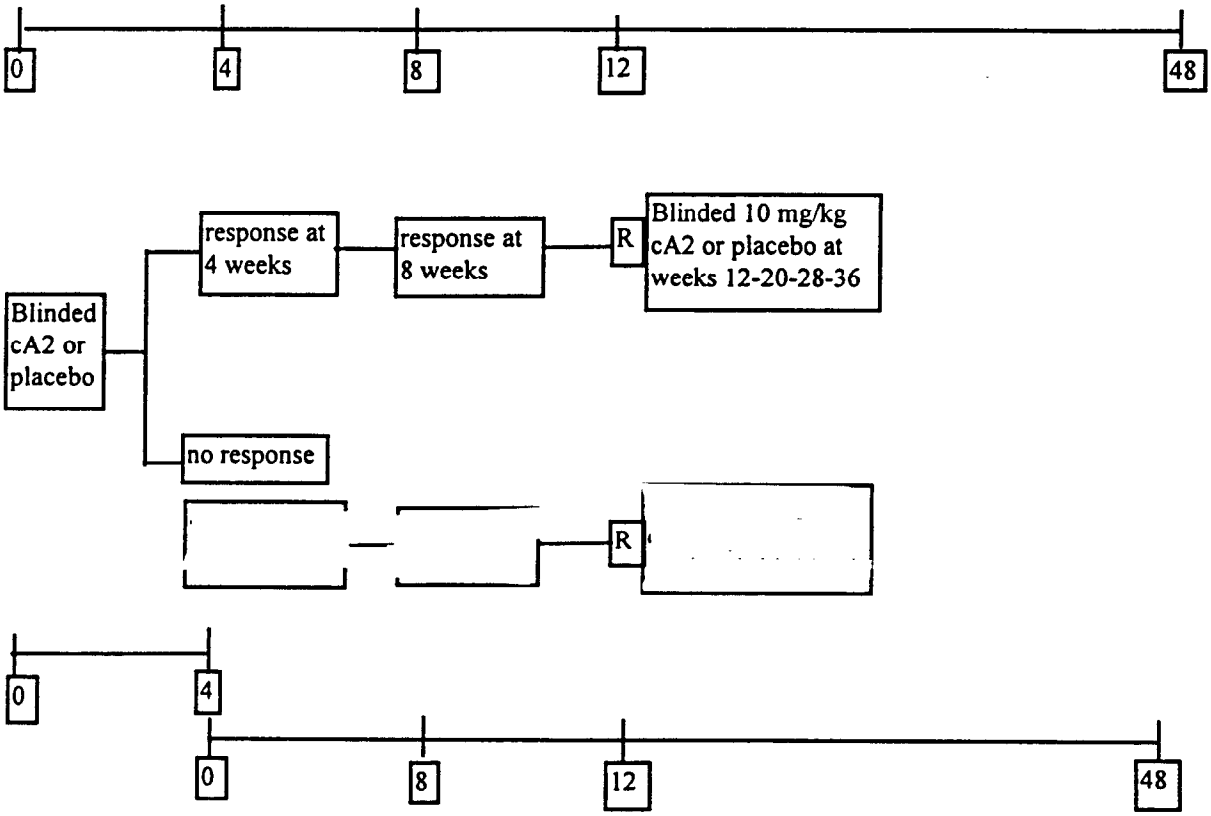
To determine the safety, tolerance, clinical and endoscopic response, immunogenicity and pharmacokinetics of a single dose of 5, 10 and 20 mg/kg of cA2 as compared to placebo in patients with active Crohn's disease.

To evaluate the safety, tolerance, clinical response and immunogenicity of subsequent repeated treatments with 10 mg/kg of cA2 compared with placebo, in patients who have shown a response to an initial treatment.

2.1.3 Study Design

This trial was designed to provide information regarding safety and efficacy in two phases: the Initial treatment phase and the . A schematic outline of the protocol is shown in Figure 1.

Figure 1. T16 Clinical Trial Design



Initial Treatment Phase: Eligible patients who had their medication(s) stabilized or washed out completed a Crohn's disease activity index (CDAI) diary card for at least 7 days prior to the screening visit. During screening, a physical examination including weight and vital signs, routine laboratory evaluations, stool culture, CXR and ECG were performed and the patient's CDAI was calculated. At the European sites, an endoscopy

was also performed. Patients were treated with study medication within 7 days of screening procedures.

Patients were randomized to either placebo, 5 mg/kg, 10 mg/kg or 20 mg/kg cA2 administered by IV infusion over 2 hours. Following administration, patients returned for clinical and laboratory assessments at weeks 2, 4, 8 and 12. An endoscopy was performed at week 4 at the European sites. Patients who did not respond at the week 4 visit were offered an open-label treatment with 10 mg/kg cA2. With the open-label infusion, the designation of follow-up times was reset and patients returned for clinical and laboratory assessments at weeks 2, 4, 8 and 12 following the open-label infusion.

2.1.4 Subjects

Inclusion Criteria:

- CDAI ≥220 and ≤400
- Men and women ≥ 18 and ≤ 65 years old
- Crohn's disease or at least 6 months' duration, with colitis, ileitis or ileocolitis confirmed by radiography or endoscopy. (Confirmation by radiography or endoscopy was deleted in amendment 1.)
- At least 1 on the following:
    - Use of oral corticosteroid therapy of ≤ 40 mg/day
    - Use or lack of response to ≥ 2 g/day of sulfasalazine or ≥ 800 mg of mesalamine.
    - Use of or lack of response to azathioprine or 6-mercaptopurine (6-MP).
    - Failure to respond to methotrexate or cyclosporine, with a stop date at least 3 months prior to screening.
- If using oral corticosteroids, sulfasalazine or mesalamine, a start date at least 8 weeks prior to screening, with a stable dose of sulfasalazine or mesalamine for at least 4 weeks prior to screening and a stable dose of oral corticosteroids for at least 2 weeks prior to screening.

  If not using oral corticosteroids, a stop date of any previous steroid regimen of at least 4 weeks prior to screening. If not using sulfasalazine, mesalamine, azathioprine or 6-MP, a stop date of any previous treatment with these agents of at least 8 weeks prior to screening.

- Screening laboratory tests

Exclusion Criteria:

- Crohn's disease limited to stomach or proximal small intestine
- Symptomatic stenosis or ileal strictures that might have required surgical intervention or that might render patients unresponsive to cA2.
- Undergoing a proctocolectomy or total colectomy with ileorectal anastomosis. Segmental colectomy was permitted.
- A stoma.
- Positive stool culture for enteric pathogens, pathogenic ova or parasites or positive stool examination for C. difficile.
- Double-stranded DNA antibodies at screening.
- Treatment with parenteral steroids or ACTH within 4 weeks prior to screening. Treatment with steroids other than those associated with conventional absorption patterns (e.g., budesonide was excluded).
- Requirement of oral or parenteral corticosteroid therapy for other disease(s), e.g., asthma.
- Concomitant use of cyclosporine or methotrexate during the 3-month period prior to screening.
- Serious infections, such as hepatitis, pneumonia or pyelonephritis, in the 3 months prior to screening.
- History of opportunistic infections such as herpes zoster within 2 months prior to screening.

2.1.5 Prior and Concomitant Therapy

Corticosteroid Therapy. Patients using oral corticosteroids when enrolled in the initial treatment phase were requested to keep their corticosteroid dosage stable until 8 weeks following the initial blinded or open-label infusion. After the week 8 evaluation, patients using corticosteroids were allowed to taper their dosage if they were responding to treatment. However, the protocol indicated that it was preferable for patients to stay at their pre-study dose of corticosteroids through the week 12 evaluation. If corticosteroid dosage was tapered, the following schedule was followed:

20-40 mg prednisone equivalent/day: taper 5 mg/5-7 days
<20 mg prednisone equivalent/day: taper 2.5 mg/5-7 days

Increasing the prednisone dosage above the baseline level was not permitted during participation in the study. If it became necessary to start prednisone or increase the dosage above the baseline level, the lack of efficacy or loss of response was required to be clearly documented by a full efficacy evaluation. No further study medication was to be given.

Other Medications for Crohn's Disease. Patients using azathioprine, 6-mercaptopurine, sulfasalazine (or equivalent) or mesalamine were requested to keep their

prescribed dosage stable throughout their participation in the study. Patients were not allowed to use cyclosporine or methotrexate during their participation in the study. If it became necessary to initiate use of 1 of these agents within 12 weeks of an infusion with study medication due to lack of efficacy or loss of response, a full efficacy evaluation was performed to document the lack of efficacy or loss of response. No further study medication was to be given. Permitted medications included antibiotics, antidiarrheal medications or other drugs for the treatment of Crohn's disease. These medications were to be administered at a stable dosage level during the first 8 weeks following the initial blinded or open-label infusion of the initial treatment phase study and preferably throughout the study.

Other Medications. Investigational drugs, including drugs other than cA2 and drugs targeted at reducing TNF (e.g., pentoxifylline or thalidomide), were not permitted during participation in the study.

2.1.6 Efficacy Evaluation

The following definitions were used to evaluate the efficacy of the treatment:

> Clinical response was defined as a reduction from baseline in the CDAI score of at least 70 points. Patients who were treated with medication not allowed by protocol because of lack of efficacy or loss of response were considered non-responders at the time of change in medication regardless of their CDAI score.
>
> Clinical remission was defined as a reduction in the CDAI score to below 150 points. Patients who were treated with medication not allowed by protocol because of lack of efficacy or loss of response were considered non-responders at the time of change in medication regardless of their CDAI score.

In addition, although not prespecified in the study protocol, if surgery or procedures related to Crohn's disease (e.g., segmental resection, dilation) were performed that could influence measurements of disease activity, they were considered to constitute a loss or lack of response.

Primary Efficacy Analysis. The primary efficacy analysis was the comparison of the proportion of patients achieving a clinical response at the 4-week evaluation.

Secondary Efficacy Analyses - Initial Treatment Phase. Secondary efficacy analyses and data summaries performed on data collected during the initial treatment phase included clinical response over time; time to loss of response; clinical remission over time; change in CDAI, IBDQ and CDEIS scores and CRP values; changes in components of the CDAI, proportion of patients discontinued and the week 12 IBDQ scores in patients who discontinued. In addition, although not prespecified by protocol, the proportion of patients who achieved at least a 100-point reduction was determined. Clinical response and clinical remission rates and changes in the CDAI, IBDQ and CRP

values were summarized for patients receiving the open-label infusion according to the initial blinded infusion that was received.

2.1.7 Evaluation of Safety

The safety of cA2 treatment was examined by tabulating adverse events. serial measurements of laboratory parameters, and vital signs. For the initial treatment phase, data collected following onset of the open-label 10 mg/kg cA2 infusion were summarized separately from the data collected following the initial blinded infusion (and up to the

. For all numeric data, values were converted to standard units with the desired number of significant digits.

2.1.8 Evaluation of HACA Responses

HACA was measured using a double-antigen EIA. In this analysis, the presence of an immune response was determined in three stages. First, the test sera were screened at a 1:10 dilution and the optical densities (ODs) of the test samples were compared with the 0.25 OD assay cutoff. In addition, the baseline and post-treatment sample ODs were compared for a 2-fold OD increase. Second, potentially positive samples were then titered to quantify the amount of immunoreactivity. Finally, potentially positive samples were tested for binding and specificity to soluble cA2. Binding was determined to be specific for cA2 if the OD was reduced ≥ 50% by 300 mcg/mL cA2. A complete description of the HACA method, validation, and criteria for positive response is provided in Attachment 4. The incidence of positive HACA responses to the study medication was summarized by the treatment groups in the initial treatment phase and the repeated treatment phase.

2.1.9 Evaluation of ANA and anti-dsDNA Results

ANA was measured by ═══ (for North-American centers) and ——— (for European centers) by indirect immunofluorescence technique (IFT) using Hep-2 cells. Sera positive

for ANA were tested for anti-dsDNA. Anti-dsDNA was measured by —— , using an EIA and by —— using the IFT on *Crithidia luciliae*.

Patients were evaluated for ANA and/or anti-dsDNA at screening and week 12 for the initial treatment phase and at week 48 for the repeated treatment phase. The incidence for ANA and anti-dsDNA was summarized by treatment group.

2.2 Results

2.2.1 Patient Disposition

A total of 108 patients from 18 study sites (13 USA and 5 European) was enrolled in T16 between 21 June 1995 and 31 October 1995. The last follow-up visit for the initial treatment phase (12 weeks after the initial blinded or open-label infusion) took place on 20 March 1996. The two most active US sites were ——— / —— n=20) and ——— (n=11). The two most active European sites were ——— —— (n=13) and ——— (n=9).

Because of the relatively small size of the clinical trial, the disposition of the patients for each of the initial blinded arms is shown in Appendix A. Review of these figures reveal the diverse differences in drug exposure among the patients.

Baseline Demographics and Clinical Characteristics. All patients were white and approximately half (50.9%) were male. Ages ranged from 20 to 65 years (median (37 years) and body weight ranged from 40 to 113.6 kg (median 67.1 kg).

Baseline clinical characteristics are summarized in Table 2. Fifty-four percent of the patients had involvement of both the ileum and colon and 76% had extra-intestinal manifestation of disease (most commonly arthralgia, arthritis, and aphthous stomatitis). Nearly half of the patients (49.1%) had previous segmental resection of the colon. The median baseline CDAI was 306, defining the majority of patients as having moderate to severe disease activity.

Table 2.Baseline Clinical Characteristics of Patients Enrolled into Clinical Trial T16

	Placebo n=25	5 mg/kg n=27	10 mg/kg n=28	20 mg/kg n=28
Disease duration - median years	9.4	11.1	9.9	13.9
Involved area:				
Ileum	8 (32%)	3 (11%)	4 (14%)	2 (7%)
Colon	7 (28%)	9 (33%)	10 (36%)	7 (25%)
Ileum & colon	10 (40%)	15 (56%)	14 (50%)	19 (68%)
Hx resections	13 (52%)	12 (44%)	14 (50%)	14 (50%)
Extra-intestinal signs	17 (68%)	19 (70%)	24 (86%)	22 (79%)
Fistulae	6 (25%)	5 (18%)	3 (11%)	6 (21%)
CDAI - median	285	306	312	308
IBDQ - median	129	118	113	113
CRP - median	0.7	1.0	0.8	1.3

Concomitant Medications. No significant differences were found with respect to concomitant medications used at baseline for Crohn's disease. Sixty percent of patients were receiving corticosteroids at baseline, with 26% of patients receiving prednisone-equivalent doses of 20 mg/kg or more; 37% were receiving 6-MP/azathioprine; and 60% were receiving aminosalicylates. No patients were enrolled who were treated with methotrexate as proscribed by the eligibility criteria. Overall 92% of patients were receiving treatment with corticosteroids, cyclosporine, 6-MP, azathiaprine and/or aminosalicylates at baseline.

A review of the concomitant medication listing revealed that 5 patients did not meet the inclusion criteria. Patient —— (10 mg/kg) was on a stable dose of prednisone for 5 days prior to enrollment instead of 2 weeks as required by protocol and Patient —— (placebo) was on a "stable" dosage of prednisone for 1 day prior to enrollment. Patient —— (placebo) changed the —— dosage from 4000 mg to 4800 mg 1 week prior to enrollment while the protocol required a stable dosage of 2 weeks. Patient —— (10 mg/kg) received cyclosporine at baseline (exclusion criteria) but the drug was tapered off during the initial treatment phase of the trial. Patient —— (10 mg/kg) received 1 dose of azathioprine 1 month prior to enrollment while the protocol required patients to be off azathioprine for 8 weeks.

Initial Treatment Phase. Table 3 shows the distribution of the patients among the initial treatment arms.

Table 3. Distribution of Patients in T16 in Initial Treatment Phase

	Placebo	5 mg/kg	10 mg/kg	20 mg/kg	Total
Patients	25	27	28	28	108

Initial Treatment Phase Dose Administration. All 108 patients enrolled received the initial infusion of blinded study drug. Two patients were assigned a treatment but did not receive treatment; 1 declined to participated and 1 did not meet eligibility criteria. By protocol, patients were considered enrolled once they received any part of the initial infusion; thus, no further data were collected in these two patients and they are not included in the analyses. None of the infusions were prematurely discontinued. The duration of initial cA2 infusions ranged from 1.5 hours to 2.8 hours.

Patients who did not respond at the week 4 visit following the initial blinded infusion received an open-label infusion with 10 mg/kg cA2. A total of 48 patients (44.4%) received the open-label infusion. The distribution of patients who received the open-label infusion by initial treatment group is summarized in Table 4.

Table 4. Distribution of Patients in T16 in Open Label Phase

	Placebo n=25	5 mg/kg n=27	10 mg/kg n=28	20 mg/kg n=28	Total n=108
Patients receiving open-label	19 (76%)	6 (22.2%)	15 (53.6%)	8 (28.6%)	48 (44.4%)

The decision to treat a patient with an open-label infusion of 10 mg/kg cA2 was made by the site based on their calculation of the baseline and week 4 CDAI score. Because of miscalculations at the study center, 3 patients (' , 5 mg/kg and ' 10 mg/kg) were incorrectly determined to have not had a clinical response and received an open-label infusion. No weight was available at week 4 for Patient ' (placebo) and therefore the CDAI could not be calculated. The patient had no improvement in clinical symptoms and received an open-label infusion.

2.2.2 Sponsor's analysis of Efficacy Data from Clinical Trial T16

2.2.2.1 Analysis of Primary Endpoint

65.1% of the cA2-treated patients achieved a clinical response (≥ 70-point reduction from baseline in the CDAI) at the week 4 evaluation compared to 16.7% of the placebo patients ($p<0.001$, Table 4). The proportion of patients who responded was significantly higher in each cA2 treatment group compared to the placebo group. There was no apparent relationship between cA2 dose and the proportion of patients responding; the highest clinical response rate was observed in the 5 mg/kg dose group (81.5%; $p<0.001$ vs placebo).

For all treatment groups, all patients enrolled were evaluated at week 4 except for one patient in the placebo cohort. One placebo patient (Patient ——, was not included in the 4-week evaluation because the patient's CDAI score could not be calculated (no body weight was obtained). This patient, who had a 40-point increase in CDAI at week 2, showed no clinical improvement and received an open-label infusion.

Table 5 shows the sponsor's analysis of the primary endpoint. In addition, the sponsor performed an analysis stratified by location of disease (ileum, colon, ileum and colon) as more patients with their disease limited to the ileum were in the placebo group (32.0%) compared to the cA2 treatment group (range 7.1% to 14.3%, $p=0.016$).

Table 5. Sponsor's Analysis of Primary Endpoint for T16

	Placebo (n=25)	**5 mg/kg** (n=27)	**10 mg/kg** (n=28)	**20 mg/kg** (n=28)	**all cA2** (n=83)
Patients evaluated	24	27	28	28	83
Number with response	4 (16.7%)	22 (81.5%)	14 (50%)	18 (64.3%)	54 (65.1%)
p-value vs. placebo		<0.001	0.045	0.002	<0.001

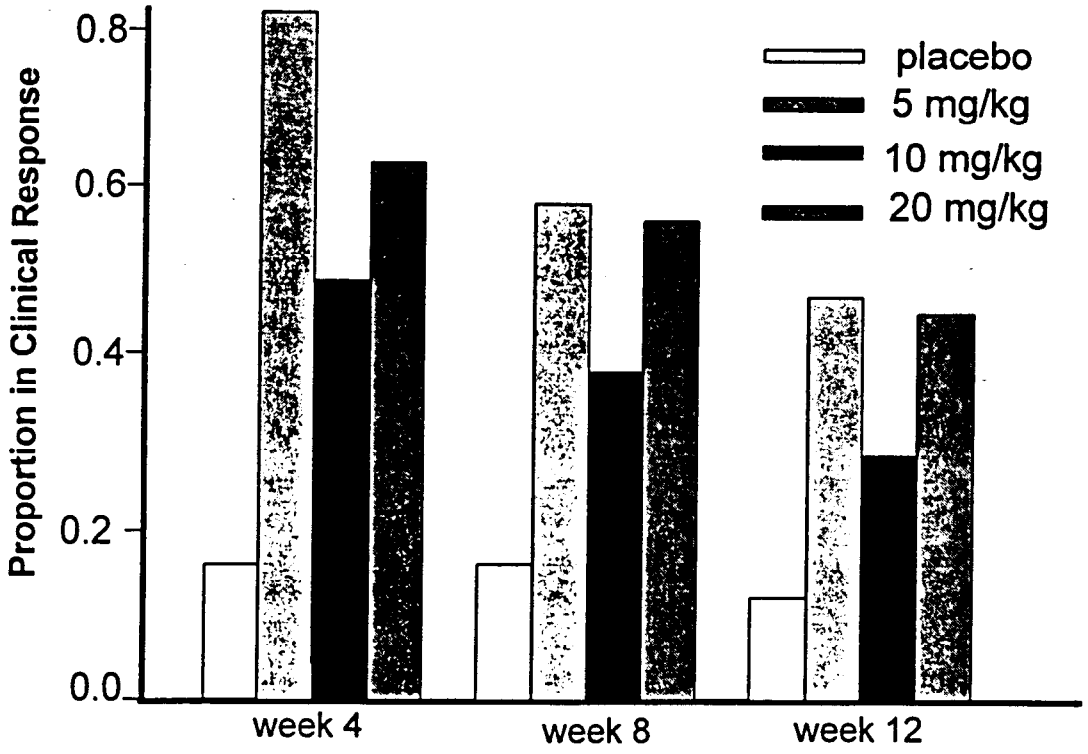
Treatment effect p-value <0.001 (chi-squared).

Maintenance of clinical response. The proportion of patients with clinical response (≥ 70-point decrease from baseline CDAI) decreased after the 4 week endpoint, i.e., no patients responded after the 4 week period. Table 6 shows the number of patients that achieved a response at the 4-week evaluation and subsequently lost their response during the initial treatment phase. Among patients who responded at the week 4 evaluation, 37.0% (20 of 54) of cA2-treated and 25.0% (1 of 4) placebo-treated patients subsequently lost response during the initial treatment phase. The proportion of patients losing response tended to be less in the 20 mg/kg cA2 group (27.8%) than in the 5 and 10 mg/kg groups (40.9% and 42.9%, respectively). Figure 2 shows the proportion of patients who responded through the 12 weeks following a single infusion of blinded study drug.

Table 6. Time to loss of response - T16

	Placebo (n=25)	**5 mg/kg** (n=27)	**10 mg/kg** (n=28)	**20 mg/kg** (n=28)
Responded at 4 weeks	4	22	14	18
Loss of response at 8 weeks	0	6	3	2
Loss of response at 12 weeks	1	3	3	3
Total	1 (25%)	9 (41%)	6 (43%)	5 (28%)

Figure 2. Clinical Response through week 12 following a single infusion.



Response of >100 point decrease in CDAI from baseline. The protocol did not prospectively define a secondary endpoint of ≥ 100-point decrease from baseline. However, a ≥ 100 point reduction from baseline in CDAI is a more stringent endpoint and one used in other clinical trials evaluating therapies for Crohn's disease. Table 7 shows the number of patients achieving a ≥ 100-point reduction from baseline in CDAI at any time during the 4-week evaluation period and at each evaluation. Using this criterion, 51.8% of the cA2-treated patients responded at week 4, compared to 16.7% of the placebo-treated patients. There was no apparent relationship between cA2 dose and the proportion of patients who responded using this criterion.

Table 7. Patients achieving ≥100-point reduction from baseline CDAI - T16

	Placebo (n=25)	**5 mg/kg** (n=27)	**10 mg/kg** (n=28)	**20 mg/kg** (n=28)
Week 4	4 (16.7%)	15 (56%)	12 (43%)	16 (57%)
Week 8	4 (16%)	14 (52%)	11 (39%)	13 (46%)
Week 12	3 (12%)	12 (44%)	8 (29%)	12 (43%)

Clinical remission following a single infusion. Clinical remission using the CDAI score has been defined as a CDAI <150. Table 8 shows the number of patients achieving a clinical remission (CDAI <150) following the initial infusion. At the 4 week evaluation, 32.5% of patients treated with cA2 achieved clinical remission compared with 4.2% of patients in the placebo group. The 5 mg/kg dose group showed the highest remission rate (48.1%) compared to the 10 and 20 mg/kg dose groups (both 25.0%). At week 8, 30.1% of the cA2 treated-patients were still in remission and 24.1% were in remission at week 12.

Table 8. Patients with clinical remission - Initial Phase T16

	Placebo (n=25)	**5 mg/kg** (n=27)	**10 mg/kg** (n=28)	**20 mg/kg** (n=28)
Week 4	1 (4%)	13 (48%)	7 (25%)	7 (25%)
Week 8	4 (16%)	10 (37%)	8 (29%)	7 (25%)
Week 12	2 (8%)	8 (30%)	5 (18%)	7 (25%)

2.2.2.2 Analysis of the open label treatment

Patients who did not respond at 4 weeks after the initial blinded infusion were offered an open-label infusion of 10 mg/kg cA2 to be administered within 2 weeks of the 4 week evaluation visit. Forty-eight (44.4%) patients received an open-label infusion; 19 patients following an initial placebo infusion and 29 patients following an initial cA2 infusion. Table 9 summarizes the clinical response rate following the open-label infusion according to the initial blinded infusion received. Among patients receiving placebo initially, the response rate at 4 weeks after the open-label infusion (58%) was similar to the response rate for all cA2-treated patients at 4 weeks after the initial blinded infusion (65%). In comparison, approximately one-third of the patients who received cA2 as their initial blinded infusion responded to a second dose of cA2 suggesting that patients who fail to respond to an initial dose of cA2 may less responsive to anti-TNF therapies.

Table 9. Clinical response to open-label cA2 treatment - T16

	Placebo + 10 mg/kg (n=19)	**5 mg/kg + 10 mg/kg** (n=6)	**10 mg/kg + 10 mg/kg** (n=15)	**20 mg/kg + 10 mg/kg** (n=8)
Week 4	19 (58%)	2 (33%)	6 (40%)	2 (25%)
Week 8	13 (68%)	3 (50%)	5 (33%)	4 (50%)
Week 12	10 (56%)	1 (17%)	5 (33%)	2 (25%)

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The adverse events for the patients treated with cA2 were:

- week 18. Mononucleosis
- week 16. Severe headache
- week 36. Hidradenitis with fever
- week 12. Severe infusion reaction; treated with steroids and antihistamines.
- week 20. Lupus syndrome; chest tightness
- week 30. Acalculus cholecystitis

The classification of "other" for placebo includes discontinuation of a patient who was noncompliant, and a patient who voluntarily withdrew.

2.2.3 FDA's Analysis of Clinical Trial T16

2.2.3.1 Initial Treatment Phase

The primary endpoint was a ≥ 70-point reduction from baseline CDAI without a change in medication or the need for surgical intervention for Crohn's disease. Table 11 shows an analysis of the primary endpoint based solely on a decrease in CDAI by ≥ 70-points from baseline. In separate analyses (not shown) treatment effect is maintained when these patients are added back to the dataset, regardless of whether they are considered failures or successes.

Table 11. Response of patients with week-4 CDAI score.

	Placebo (n=25)	**5 mg/kg** (n=27)	**10 mg/kg** (n=28)	**20 mg/kg** (n=28)
Patients evaluated	22	26	28	28
Number of patients who responded	4 (16%)	22 (85%)	14 (50%)	18 (64.3%)
p-value vs. placebo (two-sided Fisher's Exact Test)		<0.001	0.036	0.002

Treatment effect p-value <0.001 (Chi-squared test).

Time in response to a single infusion of cA2. In order to address the question regarding the clinical efficacy of a single infusion of cA2 over time, we evaluated the small cohort of patients who were randomized to cA2 in the initial treatment phase and who were: 1) responders at week 4 by the study definition, 2) received no open label cA2, and 3) were randomized to placebo at 12 weeks. There were 23 patients meeting these criteria. Rather than compare their 8-48 week CDAI scores to baseline CDAI, we attempted to measure

their responses relative to what they had achieved at the 4 week timepoint by the following criteria:

(1) As long as a patient had a CDAI score no more than 25% above their 4 week score during the retreatment phase, we classified that patient as a continued responder.

(2) We made an exception for patients who had a dramatic reduction in CDAI and achieved remission at 4 weeks (e.g., their 4 week CDAI score was 20 with a baseline CDAI >220 per protocol), and classified patients in continued response if they continued in remission (CDAI <150 rather than below a CDAI 25).

(3) Once the CDAI went above the cutoff point as defined in (1) and (2) or there was no data recorded, the patient was considered to have lost response.

These criteria are analogous to how duration of partial response is measured in the oncology setting.

For each of the 23 patients, we found the last time (in weeks) continued response. Since patients were evaluated at 4 week intervals, the time to last response was always a multiple of 4. The times (in weeks) of last response for the 23 patients:

4,4,
8,8,8,8
12,12,12,12,12
16,16,16
20
32
40,40+
44,44
48+,48+,48+

The median duration of response was 16 weeks with the majority of patients experiencing 12 weeks of response through this time period. We noted that the distribution may not be unimodal. This response of 3-4 months is what investigators of the clinical trial T8 and a single open label infusion of cA2 given to a 14 year old child on a compassionate basis reported in the literature. All nine of the patients evaluated in T8 relapsed by the third month and the child relapsed by month 4.

There appears to be a cohort of patients in which disease activity was quiescant for more than 6 months. Because of the small number of patients analyzed in this analysis, it is difficult to determine whether the improvement seen in these patients was because the single infusion of cA2 decreased the inflammation sufficiently to allow the other medications to take effect, was attributed to a single infusion cA2 alone, or was due to the

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2.2.4 Conclusions regarding T16 Efficacy Data

1. Patients who received any of the three doses of cA2 had a significantly increased chance of having a ≥ 70-point reduction from their baseline CDAI in 4 weeks than those patient treated with placebo. Many of the patients who experienced a CDAI response from a single dose of cA2 gradually lost it after 8 to 12 weeks, suggesting that repeated dosing is required to maintain an effect.

2.

3.

4.

5.

2.3. Analysis of Safety Database - Study T16

Because of the small sample size in clinical trial T16 and the comparatively small number of patients who received only placebo for comparison, analysis of the safety regarding the laboratory values (chemistry, hematology, etc.), anti-dsDNA antibody and HACA will be incorporated into the overall safety database analysis for all non-sepsis clinical trials evaluating cA2 (section 4.0). This section will review the safety data for clinical events experienced by patients enrolled in T16 in the Initial Treatment Phase and the Repeat Treatment Phase.

2.3.1 Initial Treatment Phase

All Adverse Experiences During the Initial Treatment Phase. Table 17 presents adverse experiences reported during the initial treatment phase by >2% of patients treated with cA2 (the cA2 column includes any adverse experience reported after the initial blinded infusion of cA2 or the open-label infusion of cA2). 60.0% of patients who

received placebo and 82.4% who received cA2 reported 1 or more adverse experiences. It should be noted that the average weeks of follow up of the placebo-treated patients was about one-half (6.9 weeks) of that for the cA2-treated patients (14.9 weeks). The most common adverse experiences were headache, nausea, and upper respiratory tract infection. Headache and upper respiratory tract infection was reported by a similar proportion of patients who received placebo (20.0% and 12.0%, respectively) and cA2 (21.6% and 11.8%, respectively). Nausea was reported with a slightly higher proportion of patients who received cA2 (15.7%) than those who received placebo (8.0%).

Table 17. Number of patients with any adverse experience by WHOART preferred term - Initial Treatment Phase (T16)

	Placebo (n= 25)	**All cA2 Treated Patients** (n = 102)
Avg. Weeks of follow-up	6.9	14.9
Pts with 1 or more adverse experience	15 (60.0%)	84 (82.4%)
WHOART preferred term		
Headache	5 (20.0%)	22 (21.6%)
Nausea	2 (8.0%)	16 (15.7%)
URI	3 (12.0%)	12 (11.8%)
Abdominal pain	2 (8.0%)	9 (8.8%)
Fatigue	1 (4.0%)	9 (8.8%)
Fever	2 (8.0%)	8 (7.8%)
Myalgia	1 (4.0%)	7 (6.9%)
Dizziness	2 (8.0%)	7 (6.9%)
Pharyngitis	1 (4.0%)	7 (6.9%)
Pain	0 (0.0%)	7 (6.9%)
Coughing	0 (0.0%)	6 (5.9%)
Rhinitis	1 (4.0%)	6 (5.9%)
Pruritus	1 (4.0%)	5 (4.9%)
Vomiting	0 (0.0%)	5 (4.9%)
Dyspepsia	0 (0.0%)	5 (4.9%)
Sinusitis	1 (4.0%)	5 (4.9%)
Chest pain	1 (4.0%)	5 (4.9%)
Moniliasis	0 (0.0%)	5 (4.9%)
Bronchitis	1 (4.0%)	5 (4.9%)
Arthralgia	0 (0.0%)	4 (3.9%)
Arthritis	0 (0.0%)	4 (3.9%)
Flatulence	0 (0.0%)	4 (3.9%)
Dyspnea	0 (0.0%)	4 (3.9%)
Back pain	0 (0.0%)	4 (3.9%)
Rash	0 (0.0%)	3 (2.9%)
Sweating increased	0 (0.0%)	3 (2.9%)
Constipation	0 (0.0%)	3 (2.9%)

Hypotension	0 (0.0%)	3 (2.9%)
Rash vesicular	0 (0.0%)	3 (2.9%)

Table 18 reports adverse experiences during the [illegible] according to the WHOART preferred term for >5% of events for all [illegible] Among all patients, the most frequently reported adverse experiences were upper respiratory tract infection (20.5%), headache (13.7%), abdominal pain (13.7%), and nausea (13.7%). Upper respiratory tract infection, headache and nausea were reported with a higher incidence by patients who received cA2 [illegible] than by those who received placebo (24.3% versus 16.7%, 16.2% versus 11.1% and 18.9% versus 8.3% respectively). The incidences of bronchitis, pharyngitis and fatigue, dizziness, rhinitis and dry skin were slightly higher among patients who received [illegible] among those who received placebo; the incidences of vomiting, anxiety and monoliasis were slightly higher among patients who received [illegible]

Table 18. Number of patients with any adverse experience by WHOART preferred term - [illegible] Phase - T16

	Placebo	**cA2 (10 mg/kg)**	**All [illegible] Patients**
	(n = 36)	(n = 37)	(n = 73)
Avg weeks of follow-up			
	30.7	32.5	31.6
Pts with 1 or more adverse experience			
	35 (97.2%)	35 (94.6%)	70 (95.9%)
WHOART preferred term			
URI	6 (16.7%)	9 (24.3%)	15 (20.5%)
Headache	4 (11.1%)	6 (16.2%)	10 (13.7%)
Abdominal pain	5 (13.9%)	5 (13.5%)	10 (13.7%)
Nausea	3 (8.3%)	7 (18.9%)	10 (13.7%)
Fever	5 (13.9%)	4 (10.8%)	9 (12.3%)
Bronchitis	3 (8.3%)	6 (16.2%)	9 (12.3%)

Pharyngitis	1 (2.8%)	7 (18.9%)	8 (11.0%)
Vomiting	5 (13.9%)	2 (5.4%)	7 (9.6%)
Sinusitis	4 (11.1%)	3 (8.1%)	7 (9.6%)
Fatigue	2 (5.6%)	5 (13.5%)	7 (9.6%)
Arthralgia	4 (11.1%)	2 (5.4%)	6 (8.2%)
Flu syndrome	2 (5.6%)	4 (10.8%)	6 (8.2%)
Rash	3 (8.3%)	2 (5.4%)	5 (6.8%)
Dizziness	1 (2.8%)	4 (10.8%)	5 (6.8%)
Rhinitis	1 (2.8%)	4 (10.8%)	5 (6.8%)
Pain	2 (5.6%)	3 (8.1%)	5 (6.8%)
Rash erythematous	2 (5.6%)	2 (5.4%)	4 (5.5%)
Anxiety	4 (11.1%)	0 (0.0%)	4 (5.5%)
Insomnia	2 (5.6%)	2 (5.4%)	4 (5.5%)
Laryngitis	1 (2.8%)	3 (8.1%)	4 (5.5%)
Urinary tract infection	1 (2.8%)	3 (8.1%)	4 (5.5%)
Back pain	2 (5.6%)	2 (5.4%)	4 (5.5%)

Discontinuation from the Study. Six patients, all who received [illegible] discontinued retreatment (i.e., did not receive all 4 scheduled infusions) because of adverse experiences. Of these, 1 patient discontinued treatment because of a serious reaction that occurred during infusion of the patient's second cA2 infusion.

- Patient —— (5 mg/kg + 10 mg/kg x 4) developed dyspnea, pain, abdominal pain, back pain, nausea, flushing, hypesthesia, vision abnormality and rigors immediately after the initial administration of the first and only [illegible]

The remaining 5 patients who discontinued [illegible] due to adverse experiences are detailed below:

- Patient —— (5 mg/kg + 10 mg/kg x 4) developed mononucleosis approximately 8 weeks after the [illegible] phase infusion and the third infusion was delayed. (The patient received one subsequent cA2 infusion 24 weeks after the [illegible] infusion).

- Patient —— (20 mg/kg + 10 mg/kg x 4) had cholecystitis 9 days after [illegible] infusion.

- Patient —— (20 mg/kg + 10 mg/kg + 10 mg/kg x 4) developed severe headache during the [illegible] infusion and declined further treatment.

- Patient —— (20 mg/kg + 10 mg/kg + 10 mg/kg x 4) experienced extensive hidradenitis within 2 days following the [illegible] infusion and was withdrawn from further treatment.

- Patient [redacted] (20 mg/kg + 10 mg/kg + 10 mg/kg x 4) experienced lupus arthritis almost 6 weeks after the [redacted] fusion and was withdrawn from further treatment.

One additional patient discontinued regular scheduled efficacy evaluations from the trial after the [redacted] infusion due to an adverse experience:

- Patient [redacted] (20 mg/kg + 10 mg/kg x 4) discontinued efficacy evaluations due to persistent arthralgias that were considered possibly related to study agent.

Infusion Reactions. A total of 14 patients (5 placebo and 9 cA2 [redacted] patients) had adverse experiences reported during or within 2 hours following the end of a repeated treatment phase infusion (infusion period). These adverse experiences included ventricular extrasystoles, bradycardia, fatigue, dizziness, fever and pharyngitis in placebo retreated patients and headache, hypotension, chest pain, injection site pain, dyspepsia, GI activity increased, dizziness, nausea and vomiting in cA2 retreated patients. Included in the 9 patients retreated with cA2 who had an infusion reaction was Patient [redacted] (5 mg/kg + 10 mg/kg x 4) who experienced a serious adverse experience while receiving the first cA2- [redacted] infusion (second cA2 infusion).

The adverse experiences reported were all mild or moderate in intensity with the exception of the severe adverse experiences reported in Patient [redacted] (see above).

In addition, 7 patients had adverse experiences reported on the day of the infusion but with an unknown onset time. These adverse experiences included vitamin B-12 deficiency, headache, acne and glucocorticoids increased (Cushing face) in placebo atients and pharyngitis, involuntary muscle contractions, pain, fatigue and headache in cA2 retreated patients. The adverse experiences reported were all mild or moderate in intensity with the exception of the severe headache reported in Patient [redacted]

Four infusions were temporarily interrupted: Patient [redacted] (10 mg/kg + placebo x 4) experienced dizziness and pharyngitis 18 minutes into her third repeated treatment phase placebo infusion; Patients [redacted] (10 mg/kg + 10 mg/kg x 4) and [redacted] (same treatment group) reported injection site pain during their first repeated treatment phase cA2 infusion; and Patient [redacted] (20 mg/kg + 10 mg/kg + 10 mg/kg x 4) reported nausea, chest pain and vomiting approximately 30 minutes after onset of her [redacted] phase cA2 infusion. Of the adverse experiences reported during an infusion or within 2 hours after the end of infusion or on the day of infusion but without onset time, 6 events (2 in placebo [redacted] and 4 in cA2 [redacted]) were categorized as a cardiopulmonary disorder.

Placebo

- Patient —— (placebo + 10 mg/kg + placebo x 4) experienced mild ventricular extrasystoles during the first placebo infusion that resolved 4 weeks later.

- Patient —— (5 mg/kg cA2 + placebo x 4) experienced bradycardia during the infusion that resolved 4 weeks later.

cA2 (10 mg/kg) retreatment:

- Patient —— (placebo + 10 mg/kg + 10 mg/kg x 4) experienced hypotension 30 minutes into her infusion that resolved 3.5 hours later. No hypotension was reported during the last cA2 infusion.

- Patient —— (5 mg/kg + 10 mg/kg x 4, see above) reported dyspnea during the first infusion. This was a serious event.

- Patient —— (10 mg/kg + 10 mg/kg x 4) reported mild chest pain 30 minutes into the first cA2 repeated treatment phase infusion that resolved 3 minutes later. No chest pain was reported during subsequent cA2 infusions.

- Patient —— (20 mg/kg + 10 mg/kg + 10 mg/kg x 4) experienced chest pain, nausea and vomiting approximately 30 minutes into the first and only phase infusion resulting in a 44 minute interruption of the infusion. The chest pain resolved 10 minutes after onset, the nausea and vomiting 25 and 5 minutes after onset, respectively, and the infusion was restarted and completed without any problems.

Infections. A total of 21 patients developed 1 or more infections that required antibiotic treatment during the 13 who received cA2 and 8 who received placebo The most common infections during this period were bronchitis (5 cases), urinary tract infection and sinusitis (4 cases each), upper respiratory tract infection and pharyngitis, (3 cases each). One patient had an infection that was serious (cholecystitis, Patient —— cA2 retreatment). Two patients had an infection that was still present at the last evaluation. Patient —— who presented with several symptoms, including fever, that were later attributed to B-cell lymphoma was treated with intravenous antibiotics for a presumptive infection and Patient —— who had a hydradenitis that at the last evaluation, 3 months after its onset, was still present and treated with antibiotics. Table 19 reports the patient identification numbers and the type of infection (shown in parentheses) for patients having infections requiring antibiotic therapy.

Table 19. Patients with infections requiring oral or parenteral antibiotic treatment - Phase - T16

Placebo	cA2 (10 mg/kg)
(bronchitis, sinusitis)	(URI)
(UTI, URI)	(bronchitis)
(cellulitis)	(UTI)
fever)	(UTI)
monoliasis, URI)	(laryngitis, sinusitis, bronchitis, pharyngitis)
sinusitis)	(hydradenitis)
monoliasis)	(cystitis, rhinitis)
(flu syndrome)	(coughing, sinusitis)
	(herpes zoster)
	(bronchitis)
	(cholecystitis, otitis)
	(dysuria, pharyngitis (3x), laryngitis)
	(bronchitis, UTI)

Serious Adverse Experiences. A total of 9 patients, 4 (10.8%) who received cA2 and 5 (13.9%) who received r , had serious adverse experiences during the . Four patients had serious adverse experiences that were assessed as possibly, probably or definitely related to the study agent. Patient had thrombocytopenia, fever, splenomegaly, splenic and kidney infarction, syncope and lymphoma; Patient shortness of breath; Patient acalculous cholecystitis; and Patient lupus erythematosus (LE) syndrome.

- Patient (placebo + 10 mg/kg + placebo x 4) developed malaise, fatigue, dry cough and low grade fever approximately 4 weeks after his phase infusion. The patient was admitted for evaluation and empiric antibiotic therapy. Despite extensive diagnostic evaluation, no clear etiology could be established. An abdominal CT scan revealed splenomegaly with splenic and renal infarcts. Thrombocytopenia and anemia were noted and a splenectomy was performed. The spleen pathology was inconsistent with lymphoma and the patient was discharged. Shortly after this admission, the patient was readmitted and following an endoscopy, the pathology of a duodenal polyp biopsy revealed intravascular B-cell lymphoma (9½ months after the single 10 mg/kg infusion). The patient was treated with chemotherapy. Shortly after the patient's last study evaluation the patient developed sepsis secondary to chemotherapy and expired due to cardiac arrest.

- Patient (5 mg/kg + 10 mg/kg x 4) developed shortness of breath; numbness of the lips and the left arm; pain in the abdomen, hip, knee and back; and flushing; nausea and chills 2 minutes into the first cA2 The infusion was discontinued and the patient treated with intravenous antihistamine and corticosteroids. The shortness of breath was

assessed as a serious adverse experience. This patient had developed a positive HACA (titer of 1:80) in the sample obtained 12 weeks following the initial infusion of 5 mg/kg cA2 and before the [illegible] with 10 mg/kg.

- Patient [illegible] (20 mg/kg + 10 mg/kg x 4) developed upper abdominal pain that increased after meals beginning 9 days after the third and final [illegible] phase infusion. The patient was admitted and diagnosed with acalculous cholecystitis. The patient was treated with intravenous antibiotics and was then switched to oral therapy with resolution of the cholecystitis 8 days later.

- Patient [illegible] (20 mg/kg + 10 mg/kg + 10 mg/kg x 4) developed joint pain and swelling in the ankles, feet, toes wrists, knees and shoulders approximately 6 weeks after the patient's first and only cA2 [illegible] phase infusion. The patient's ANA was positive (1:640) at that time while negative at study entry. Double-stranded DNA antibodies were negative at the central laboratory and positive (40 IU/mL; normal 0-24 IU/mL) at the local lab. The patient was diagnosed with lupus arthritis and started on prednisone. At the last evaluation, 14 weeks later, the patient's symptoms were still present. A phone contact with the site revealed that the symptoms were resolved within 6 months after the last infusion.

The 5 patients with serious adverse experiences that were assessed as probably not related to the study agent are:

- Patient [illegible] (5 mg/kg + placebo x 4) was admitted with a duodenal stricture 5 weeks following the second and final placebo [illegible] phase infusion. The patient was treated with total parenteral nutrition and intravenous steroids and discharged 1 week later.

- Patient [illegible] (10 mg/kg + placebo x 4) developed abdominal pain, dehydration, diarrhea, fever and proctalgia approximately 7 weeks after the second and final placebo [illegible] phase infusion and was admitted. The patient was treated with methotrexate, antibiotics and bowel rest and was discharged 1 month later.

- Patient [illegible] (20 mg/kg + placebo x 4) developed abdominal pain approximately 6 weeks after the first and only placebo [illegible] infusion. The patient was hospitalized and treated with antibiotics and the dosage of prednisone was increased. Seven days later the patient was discharged in stable condition.

- Patient [illegible] (10 mg/kg + 10 mg/kg + placebo x 4) experienced worsening of Crohn's disease after the first and only [illegible] phase infusion while tapering corticosteroids. During preparation for a colonoscopy 3 weeks after the first placebo [illegible] phase infusion the patient developed abdominal cramps and diarrhea, leading to dehydration. The patient was admitted and treated

with antibiotics and bowel rest. The symptoms improved and the patient was discharged 6 days later.

- Patient placebo + 10 mg/kg + 10 mg/kg x 4) developed nausea and vomiting approximately 10 weeks after the hase infusion. The patient was admitted for examination and with the exception of irritation of the antral muscosa found during gastroscopy no abnormalities were found. After a psychiatric consultation a diagnosis of psychogenic vomiting was made and the patient was started on an antidepressant. Nine days after admission the patient was discharged with subsidence of symptoms.

Table 20. Number of patients with any serious adverse experience by WHOART preferred term - Phase - T16

	Placebo	cA2 (10 mg/kg)	All Patients
	(n = 36)	(n = 37)	(n = 73)
Avg weeks of follow-up			
	30.7	32.5	31.6
Pts with 1 or more serious adverse experience			
	5 (13.9%)	4 (10.8%)	9 (12.3%)
WHOART preferred term			
Abdominal pain	2 (5.6%)	0 (0.0%)	2 (2.7%)
Dehydration	2 (5.6%)	0 (0.0%)	2 (2.7%)
Fever	2 (5.6%)	0 (0.0%)	2 (2.7%)
LE syndrome	0 (0.0%)	1 (2.7%)	1 (1.4%)
Diarrhea	1 (2.8%)	0 (0.0%)	1 (1.4%)
Syncope	1 (2.8%)	0 (0.0%)	1 (1.4%)
Vomiting	0 (0.0%)	1 (2.7%)	1 (1.4%)
Intestinal stenosis	1 (2.8%)	0 (0.0%)	1 (1.4%)
Nausea	0 (0.0%)	1 (2.7%)	1 (1.4%)
Cholecystitis	0 (0.0%)	1 (2.7%)	1 (1.4%)
Dyspnea	0 (0.0%)	1 (2.7%)	1 (1.4%)
Splenomegaly	1 (2.8%)	0 (0.0%)	1 (1.4%)
Thrombocytopenia	1 (2.8%)	0 (0.0%)	1 (1.4%)
Proctalgia	1 (2.8%)	0 (0.0%)	1 (1.4%)
Splenic infarction	1 (2.8%)	0 (0.0%)	1 (1.4%)
Kidney infarction	1 (2.8%)	0 (0.0%)	1 (1.4%)
Lymphoma	1 (2.8%)	0 (0.0%)	1 (1.4%)

Adverse experiences are listed in decreasing order of incidence for all patients.

2.3.3. Conclusions from the safety database for clinical trial T16.

1. No specific conclusions regarding safety can be made after review of the safety database for clinical trial T16 because of the overall small number of patients, the differences in drug exposure and the lack of a true placebo for comparison.

2. There appear to be no adverse reactions specific to patients with moderate to severe Crohn's disease during acute administration. The increased occurrence of infusion reactions and serious infections requires further investigation in order to ascertain their association with cA2 infusion.

3.0. Study T20. A placebo controlled, repeated-dose study of anti-TNF chimeric monoclonal antibody (cA2) in the treatment of patients with enterocutaneous fistulae as a complication of Crohn's disease.

3.1 Study Proposal

3.1.1 Background

The T20 clinical trial is the only clinical trial conducted to support administration of cA2 to "close" enterocutaneous fistulae.

3.1.2 Objectives

To evaluate the efficacy and safety of cA2 compared with placebo in "closure" of enterocutaneous fistulae in patients with Crohn's disease.

3.1.3 Study Design

This trial was a multicenter, placebo-controlled, double-blind, parallel group, 3-arm trial in Crohn's disease patients with draining enterocutaneous (perianal and abdominal) fistulae as a complication of Crohn's disease. A total of 96 patients with draining fistulae for at least 3 months who met the inclusion/exclusion criteria were to be randomized to the following treatment groups: 10 mg/kg, 5 mg/kg, or placebo. The infusions were administered at weeks 0, 2 and 6.

Following the first infusion of study medication, patients returned for clinical and/or laboratory assessments at weeks 2, 6, 10, 14 and 18. Response evaluations consisted of examination of the enterocutaneous fistula(e), a global disease assessment, the perianal disease activity index (PDAI) in those patients who had perianal disease at baseline, and the Crohn's disease activity index (CDAI). Photographs were taken of the enterocutaneous fistula(e) at each evaluation visit, if consent was given by the patient.

Patients who showed a response at weeks 14 and 18 were asked to return to the clinic for an examination of fistula(e) at weeks 22 and 26. In addition, per Amendment 4, patients returned to have blood drawn at weeks 26 and 34 to determine human antichimeric antibody (HACA) responses.

Concomitant medications for the treatment of enterocutaneous fistulae (i.e., antibiotics, aminosalicylates, corticosteroids, azathioprine/6-mercaptopurine, and/or methotrexate) were allowed as long as patients were on a stable dosage prior to enrollment and kept their dosage stable through their participation in the study. Patients treated with corticosteroids were allowed to taper their dosage following the 6-week evaluation visit. Cyclosporine was not to be given in the study.

3.1.4 Protocol Amendments

Amendment 1: (implemented before the first patient was enrolled)

- modified the entry criteria:
  - the requirement of a stable dosage of aminosalicylates for at least 4 weeks prior to enrollment (if taken as concurrent therapy) or if not taken as concurrent therapy the drug should have been discontinued for at least 4 weeks prior to enrollment
  - surgical drainage of any abscesses had to have taken place at least 3 weeks prior to enrollment
  - in patients with a stoma, the stoma had to be present for at least 6 months prior to enrollment
  - patients with a seton were excluded, unless the seton was removed 4 weeks prior to enrollment
- added efficacy evaluations to the final evaluation in patients who discontinued from the study or had a status change (i.e., no longer being followed for efficacy evaluations)
- patient enrollment number was to be given at the time the patient was randomized, since the primary analysis in this study would be performed according to the intention-to-treat principle
- revision of the definition for a closed fistula, the primary study endpoint. The definition of a "closed" fistula was changed from one with visual closure to one that was no longer draining with gentle compression.
- addition of a quality-of-life assessment, the PDAI, which was to be performed in patients with perianal disease and serial magnetic resonance imaging (MRI) of the fistulae was to be encouraged whenever feasible
- the steroid dose units in patients receiving oral prednisone at study entry were corrected to mg/day instead of mg/kg
- other changes made in the amendment were related to the storage, preparation and administration of the cA2/placebo. (The range of temperatures for storage of drug supplies was specified (i.e., 2(C to 30(C). A precaution to avoid contact of the reconstituted study medication with plasticized polyvinyl chloride (PVC) equipment or devices during preparation or administration was added. Statements regarding the time interval during which cA2 should be administered to the patient after it had been reconstituted were modified).

Amendment 2: (was implemented before the first patient was enrolled)
This amendment was written to change the dose/dosing regimen. The original protocol was to compare a partially weight adjusted dose of approximately 10 mg/kg of cA2 administered at weeks 0 and 2 to the same dose of cA2 administered at weeks 0, 2 and 6. It was determined that better information would be obtained by evaluating different doses of cA2, rather than the same dose administered over a longer study interval. To better compare the two different doses of cA2, a fully weight-adjusted dose regimen was used. Therefore, the protocol was modified to compare a 5 mg/kg and 10 mg/kg dose of cA2,

administered at weeks 0, 2 and 6. The amendment also specified that prior to a surgery related to Crohn's disease, a full efficacy evaluation had to be performed and no further study medication was to be given.

Amendment 3: This amendment was written to increase the number of patients enrolled in the study from approximately 75 to 96, due to the unexpectedly high number of patients identified by the investigators during the last week patients were accepted for enrollment and to prevent any selection bias in accepting patients for enrollment. Amendment 3 was implemented upon receipt at the site.

Amendment 4: This amendment was written to add 2 late sampling time points (weeks 26 and 34) for HACA because cA2 present in the serum interferes with the detection of HACA. Amendment 4 was implemented after some patients had reached week 26.

Amendment 5: This amendment was written to obtain additional information on duration of response. An additional late efficacy follow-up visit for all patients was added 52 weeks after the first infusion. The visit included determining the number of open/closed fistulae and photographing of the fistulae. Amendment 5 was implemented after some patients had reached week 52.

3.1.5 Subjects

Inclusion Criteria:

- Crohn's disease of at least 3 months duration confirmed by radiography or endoscopy.
- Single or multiple draining enterocutaneous (including perianal fistulae) of at least 3 months duration. All fistulae should have been separate and distinctly identifiable.
- Age of $\geq$ 18 and $\leq$ 65 years.
- If treated with oral prednisone (or equivalent), the dose must have been $\geq$ 40 mg/day and must have been stable for at least 3 weeks prior to enrollment. If currently not treated with oral prednisone, the stop date must have been at least 4 weeks prior to enrollment.
- If treated with methotrexate, the start date must have been at least 3 months prior to enrollment. The dose must have been stable for at least 4 weeks prior to enrollment. If currently not treated with methotrexate, the stop date must have been at least 4 weeks prior to enrollment.
- If treated with 6-mercaptopurine or azathioprine, the start date must have been at least 6 months prior to enrollment. The dose must have been stable for at least 8 weeks prior to enrollment. If currently not treated with 6-mercaptopurine or azathioprine, the stop date must have been at least 4 weeks prior to enrollment.

- If treated with antibiotics, the dose must have been stable for at least 4 weeks prior to enrollment. If currently not treated with antibiotics, the stop date must have been at least 4 weeks prior to enrollment. Excluded from these criteria were antibiotics used for reasons other than Crohn's disease, i.e., mild infections like urinary tract infection.

- If treated with aminosalicylates, the dose must have been stable for at least 4 weeks prior to enrollment. If currently not treated with aminosalicylates, the stop date must have been at least 4 weeks prior to enrollment.

- Screening laboratory tests.

Exclusion Criteria:

- Local complications of Crohn's disease such as strictures or abscesses that might have confounded the evaluations of benefit from cA2 treatment. Abscesses should have been drained prior to enrollment, with at least 3 weeks between drainage of the abscess and enrollment.

- Positive pregnancy test or a planned pregnancy within the 7.5 months following the first infusion (i.e., approximately 6 months following the last infusion).

- Treatment with cyclosporine within 4 weeks of enrollment.

- Treatment with total parenteral nutrition or tube feeding.

- Use of any investigational drug within 3 months of enrollment.

- Treatment with any other therapeutic agent targeted at reducing TNF (e.g.,pentoxifylline or thalidomide) within 3 months of enrollment.

- Prior administration of cA2.

- A history of known allergies to murine proteins.

- Serious infections, such as hepatitis, pneumonia, pyelonephritis in the previous 3 months. Less serious infections in the previous 3 months, such as acute upper respiratory tract infection (colds) or uncomplicated urinary tract infection, need not have been considered exclusions at the discretion of the investigator.

- History of opportunistic infections such as herpes zoster within 2 months of screening. Evidence of active cytomegalovirus (CMV), active pneumocystis carinii, drug resistant atypical mycobacterium, etc.

- Documented human immunodeficiency syndrome (HIV) infection, ARC (AIDS related complex) or acquired immune deficiency syndrome (AIDS).

- Signs or symptoms of severe, progressive or uncontrolled renal, hepatic, hematologic, endocrine, pulmonary, cardiac, neurologic or cerebral disease.

- Known malignancy or any history of malignancy within the past 5 years.

- Stoma present for less than 6 months prior to enrollment.

- Seton present within the 4 weeks prior

3.1.6 Prior and Concomitant Therapy

Immunomodulatory Agents. Patients who used azathioprine or 6-mercaptopurine when enrolled in the study were required to have used the drugs for at least 6 months prior to enrollment, with a stable dosage of at least 8 weeks. Following enrollment, patients were required to keep their prescribed dosage stable throughout their participation in the study.

Patients who used methotrexate when enrolled were required to have been on methotrexate for at least 3 months prior to enrollment, with a stable dosage for at least 4 weeks. Following enrollment, the patients were required to keep their prescribed dosage stable throughout their participation in the study.

The use of cyclosporine was prohibited from 4 weeks prior to enrollment through the end of participation in the study.

If, because of lack of efficacy or loss of response, it became necessary to start any of the above immunologic agents or to increase the dosage, the lack of efficacy or loss of response was required to be clearly documented by a full efficacy evaluation. In this case, no further study treatment was allowed.

Corticosteroids. Patients who used oral prednisone (or equivalent) when enrolled in the study were required to be on a dosage of <40 mg/day and were required to have been on a stable dosage for at least 3 weeks prior to enrollment. Following enrollment, patients had to keep their prescribed dosage stable until the week 6 visit. If the dosage could be tapered after that visit, the following schedule was required:

20-40 mg prednisone equivalent/day: taper 5 mg/week
< 20 mg prednisone equivalent/day: taper 2.5 mg/week

Increasing the prednisone dosage above the baseline level was not permitted during study participation. If, because of lack of efficacy or loss of response, it became necessary to start prednisone or increase the dosage above the baseline level, the lack of efficacy or

loss of response was required to be clearly documented by a full efficacy evaluation. In this case, no further study treatment was allowed.

Other Medications for Crohn's Disease. Patients using aminosalicylates or antibiotics at enrollment had to keep their prescribed dosage stable throughout their participation. If treated with these drugs, the dose had to be stable for at least 4 weeks prior to enrollment. If not treated with these drugs, the stop date had to be at least 4 weeks prior to enrollment.

If, because of lack of efficacy or loss of response, it became necessary to start any of these drugs, the lack of efficacy or loss of response was required to be clearly documented by a full efficacy evaluation. No further study treatment was allowed in this case. Excluded were antibiotics given for reasons other than Crohn's disease, e.g., urinary tract infection.

Antidiarrheal and antispasmodic drugs were allowed as required.

Other Medications. Investigational drugs, including drugs other than cA2, targeted at reducing TNF (e.g., pentoxifylline or thalidomide) were not allowed during participation in the study.

3.1.7 Efficacy Evaluation

Clinical Response. At screening and during each follow-up visit (if applicable prior to infusion) the number of draining fistulae, patient's global assessment, CDAI and PDAI were assessed. For those patients who at weeks 14 and 18 had a $\geq$ 50% reduction from baseline in the number of draining fistulae, the numbers of draining fistulae were assessed at 4 week intervals until week 26 or loss of response, whichever occurred earlier.

In the original protocol a fistula was defined as close when there was no visible fistula. As defined in Amendment 1 (instituted prior to the start of the clinical trial), a fistula was considered to be closed when it no longer drained with gentle compression.

Although not required in the protocol, MRI's were encouraged whenever feasible. The sponsor informed the agency that about 24 patients in Europe had MRI's but the results of these scans have not been analyzed.

Primary Efficacy Analysis. The primary efficacy response was defined as a $\geq$ 50% reduction from baseline in the number of draining fistulae for at least 2 consecutive evaluation visits (i.e., at least 1 month) that was not accompanied by initiation or increase of any of the therapies specified in the protocol or a surgical procedure related to Crohn's disease (drainage of a perianal abscess excluded).

A fistula was considered to be closed when it no longer drained with gentle compression. Fistulae draining less than 3 months at baseline were excluded. However, all newly draining fistulae observed at a follow-up evaluation were included. For a patient with

multiple draining fistulae, the same fistulae were not required to have remained closed at the consecutive visits to achieve the primary endpoint. If a patient had a single draining fistula of at least 3 months' duration at baseline, the primary endpoint was achieved when that fistula was closed for at least 2 consecutive evaluations. To meet the primary endpoint, the first and the last of the consecutive visits were required to be at least 21 days apart.

Secondary Efficacy Analyses

Complete Response: Complete response was defined as the absence of any draining fistulae. Those patients who had a medication change not permitted by protocol or surgery related to Crohn's disease were considered to have no treatment response at any evaluation visit scheduled after the date of the medication change or surgical procedure.

Onset of Response: In patients achieving the primary endpoint, the time to onset of this response was calculated as the time in days to the first of the consecutive evaluations at which a reduction from baseline of $\geq$ 50% in the number of open fistulae was observed.

Duration of Response: Duration of response was defined as the maximum number of consecutive visits at which the patient had a reduction from baseline of $\geq$ 50% in the number of draining fistulae. Patients who had a reduction from baseline of $\geq$ 50% in the number of draining fistulae at a single visit (or at more than 1 non-consecutive visit) had a duration of response of zero. Those patients who had a medication change not permitted by protocol or surgery related to Crohn's disease were considered to have no treatment response at any evaluation visit scheduled after the date of the medication change or surgical procedure.

In addition, clinical response and clinical remission were defined for the secondary analyses on CDAI data:

Clinical response: In patients with a baseline CDAI of $\geq$ 220, a clinical response was defined as a 70-point reduction in CDAI compared to baseline. Those patients who had a medication change not permitted by protocol or surgery related to Crohn's disease were considered as non-responders from that time forward. This definition of clinical response was employed in T16.

Clinical remission: In patients with a baseline CDAI $\geq$ 150, a clinical remission was defined as a CDAI score below 150. Those patients who had a medication change not permitted by protocol or surgery related to Crohn's disease were considered as non-responders from that time forward.

3.1.8 Evaluation of Safety

All patients who were enrolled in the study were evaluated for safety. Subjects were monitored at baseline, during the infusion of study medication and at specified intervals

following the infusion. Safety measurements during the study period included ongoing assessment of adverse experiences and measurements of vital signs, hematology and clinical chemistry parameters.

Evaluation of HACA Responses. HACA was measured using a double-antigen EIA. In this analysis, the presence of an immune response was determined in three stages. First, the test sera were screened at a 1:10 dilution and the optical densities (OD) of the test samples were compared with the 0.25 OD assay cutoff. In addition, the baseline and post-treatment sample ODs were compared for a 2-fold OD increase. Second, potentially positive samples were then titered to quantify the amount of immunoreactivity. Finally, potentially positive samples were tested for binding and specificity to soluble cA2. Binding was determined to be specific for cA2 if the OD was reduced $\geq$ 50% by at least 300 mcg/mL cA2.

Patients were evaluated for HACA formation at weeks 2, 6, 10, 14, 18, 26 and 34. Because serum cA2 interferes with the detection of HACA in the HACA assay, samples for evaluating HACA were collected late to permit determination of HACA in the absence of cA2 in the serum. For the patients who discontinued treatment early, sampling was done at 12 weeks, 20 weeks and 28 weeks following the last infusion received. The incidence of HACA responses to cA2 through week 34 was summarized by cA2 treatment group.

Evaluation of ANA and anti-dsDNA Results. Serum samples were evaluated for ANA and/or anti-dsDNA using samples obtained prior to infusion at week 0 and at weeks 10 and 18. If a sample was positive for anti-dsDNA at week 18, the week 34 sample (or the week 26 sample if a week 34 sample was not available) was also tested for ANA and/or anti-dsDNA. The incidence of positive ANA and anti-dsDNA results was summarized by treatment group.

3.2 Results

Patient Disposition. A total of 94 patients from 12 study sites (7 US and 5 European) were enrolled between May 30, 1996 and October 1, 1996. The last clinical evaluation (week 26) occurred on March 31, 1997. The two most active US sites were [redacted] (n=13) and [redacted] (n=14). The two most active European sites were [redacted] (n=18) and [redacted] (n=16).

Table 21 shows the number of patients enrolled per treatment group. All patients randomized received their assigned treatment.

Table 21. Distribution of patients in treatment groups for T20.

Placebo	5 mg/kg	10 mg/kg	All patients
31	31	32	94

Baseline Demographics and Clinical Characteristics. Eighty-six (91.5%) of the 94 patients were white and the remaining 8 patients (8.5%) were black. Fifty patients (53.2%) were female and 44 (46.8%) were male. The age ranged from 18.0 to 63.0 years (median 35.0 years) and the body weight ranged from 39.3 to 103.5 kg (median 67.5 kg). There were no significant differences among the groups with respect to demographic characteristics.

Baseline clinical characteristics are summarized in Table 22. For all patients, the duration of Crohn's disease ranged from 1.2 to 37.1 years (median 11.5 years). Most patients (56.4%) had their disease localized in both the ileum and colon, and the fewest patients (14.9%) had their disease localized in the ileum only. More than 50% of the patient population had at least one segmental resection (partial or complete) of the intestine prior to enrollment. Extra-intestinal manifestations of Crohn's disease were observed in 32 patients (34.0%). The extra-intestinal symptoms most commonly present were arthralgia and arthritis. A small proportion of patients (12.8%) had a stoma.

Of the 94 patients enrolled, 42 (44.7%) had 1 draining fistula of at least 3 months' duration and 52 (55.3%) more than 1 draining fistula. Among patients with more than 1 fistula, a median of 3 fistulae was observed. Eighty-five of the patients (90.4%) had perianal fistulae and 9 (9.6%) abdominal fistulae. The majority of patients had a maximum duration of drainage of any fistula for more than 1 year. A total of 29 patients had an endoscopy within 6 months of enrollment and were evaluated for the presence of proctitis. Twelve patients (41.4%) had proctitis; all of these patients had perianal fistulae.

The Crohn's disease activity index (CDAI) was calculated for patients without a stoma. In the patients evaluated at baseline (79 out of 94 [84.0%]) the CDAI ranged from as low as 30.0 to as high as 398.0. Although all patients had fistulizing Crohn's disease, the overall disease activity in this patient population was mild, as measured by the CDAI, with a median CDAI score of 167.0 for the study population (active disease is defined as CDAI $\geq$ 150).

Among the 83 patients with perianal disease (perianal fissure, fistulae or ulcers) who were evaluated, the baseline, perianal disease activity index (PDAI) ranged from 3.0 to 19.0 (median 9.0).

There were no significant differences with respect to baseline disease characteristics across the treatment groups. For segmental resections however, there was a trend for a higher proportion of cA2-treated patients having had surgery (67.7% and 53.1% in the 5 mg/kg and 10 mg/kg cA2 groups, respectively) than placebo patients (38.7%, p= 0.074).

Table 22. Patient Characteristics in Clinical Trial T20.

	Placebo n=31	5 mg/kg n=31	10 mg/kg n=32
Disease duration - median years	11.6	13.7	10.6
Involved area:			
Ileum	3 (10%)	7 (23%)	4 (13%)
Colon	9 (29%)	7 (23%)	10 (33%)
Ileum & colon	19 (61%)	16 (52%)	18 (56%)
Hx resections	12(39%)	21 (68%)	17 (53%)
Extra-intestinal signs	11 (36%)	9 (29%)	12 (38%)
Stomas	4 (13%)	4 (13%)	4 (13%)
Fistulae			
1 fistula	13 (42%)	15 (48%)	14 (44%)
>1 fistula	18 (58%)	16 (52%)	18 (56%)
Fistula location			
Perianal	29 (94%)	27 (87%)	29 (91%)
Abdominal	2 (7%)	4 (13%)	3 (9%)
Both	0	0	0
CDAI - median	162	163	203
PDAI - median	9.0	8.0	10.0

Concomitant Medications. Thirty-three patients (35.1%) were treated with corticosteroids, with one-third of these patients (11.7%) being treated with a prednisone equivalent dosage above 20 mg/day. Thirty-eight patients (40.4%) were treated with either 6-mercaptopurine or azathioprine. Although concomitant methotrexate was permitted, none of the patients were treated with this drug. Oral aminosalicylates were used by 52 patients (55.3%) and antibiotics (metronidazole or ciprofloxacin) by 28 of the patients (29.8%). Additional concomitant medications, including rectal corticosteroids, rectal aminosalicylates, antidiarrheals and narcotic and opioid analgesics were used in a relatively small number of patients. Overall 83.0% of patients were receiving treatment with corticosteroids, 6-mercaptopurine, azathioprine, aminosalicylates and/or antibiotics at baseline.

There were no significant differences with respect to concomitant medication.

3.3 Sponsor's Analysis of the Efficacy Data

3.3.1 Primary Analysis.

The number of patients achieving the primary endpoint (a ≥ 50% reduction in draining fistulae for at least 2 consecutive visits [i.e., 1 month]) is shown in Table 23. Thirty-nine

of the 63 cA2-treated patients (61.9%) achieved the primary endpoint compared to 8 of 31 patients (25.8%) in the placebo group (p= 0.002).

Table 23. Patients achieving ≥ 50% reduction in number of draining fistulae (T20)

	Placebo (n=31)	5 mg/kg (n=31)	10 mg/kg (n=32)
Primary endpoint: ≥ 50% reduction in draining fistulae	8 (26%)	21 (68%)	18 (56%)
p-value vs. placebo		0.002	0.021

Dose response p-value = 0.017 (chi-squared test)

3.3.2 Secondary Analyses

Complete Response. Table 24 shows the number of patients with a complete response over 2 consecutive visits (i.e., 1 month). Twenty-nine of the 63 cA2-treated patients (46.0%) compared to 4 of the 31 placebo patients (12.9%) showed a complete response for at least 2 consecutive visits. The 5 mg/kg dose group had a higher response rate than the 10 mg/kg dose group (54.8% vs 37.5%). The response rates for complete response show that nearly 75% of the cA2-treated patients who achieved the primary endpoint, achieved a complete response and had no draining fistulae for at least 2 consecutive visits.

It should be noted that a complete response occurred with cA2-treatment in patients with both single and multiple fistulae; of the 29 cA2-treated patients who achieved a complete response, 15 patients had 1 draining fistula at baseline and 14 patients had more than 1 draining fistulae.

Table 24. Complete response for at least 2 consecutive visits

	Placebo (n=31)	5 mg/kg (n=31)	10 mg/kg (n=32)
complete response	4 (13%)	17 (55%)	12 (38%)
p-value vs. placebo		0.001	0.041

Dose response p-value = 0.045

Onset of Response. In patients achieving the primary endpoint, the time to onset of response was calculated as the time in days from the week 0 infusion to the first of the consecutive visits at which this endpoint was observed. The time to onset of response by treatment group is summarized in Table 25.

The median time to onset of response was shorter in the cA2-treated patients who responded to treatment compared to the placebo-treated patients who responded to treatment. The median time of both cA2 dose groups was the same and corresponded with the first evaluation visit at week 2 (14 days). In contrast, the median time to onset of

response for placebo-treated patients was 42 days, corresponding with the week 6 evaluation visit.

Table 25. Onset of response (T20)

	Placebo (n=31)	5 mg/kg (n=31)	10 mg/kg (n=32)
Pts w/primary endpoint	8	21	18
mean time to onset	47 ± 37	33 ± 27	25 ± 22
median days to onset	42	14	14

Duration of Response for the 18-week Follow-up Period. Table 26 shows the duration of response (in days) in patients who achieved the primary endpoint within the 18 week study period. The median duration of benefit was approximately 3 months across all treatment groups. (It should be noted that maximum duration of response for the 18-week follow-up period was 16 weeks [approximately 112 days] because the first post treatment evaluation was at 2 weeks and the last at 18 weeks.) Patients receiving the 10 mg/kg cA2 treatment who achieved the primary endpoint tended to have a longer duration of benefit than patients receiving the 5 mg/kg cA2 treatment (99 days vs 84 days). Patients receiving 5 mg/kg had a duration of response comparable to patients receiving placebo.

Table 26. Duration of response during the 18 week study period in patients who achieved the primary endpoint - T20

	Placebo (n=31)	5 mg/kg (n=31)	10 mg/kg (n=32)
Pts w/primary endpoint	8	21	18
mean duration	79 ± 37	7[illegible] ± 35	91 ± 29
median duration	86	84	99

Crohn's Disease Activity Index. The CDAI was obtained in 79 of the 94 patients (84%). Patients with a stoma were excluded because these patients are not able to assess the number of liquid or soft stools (1 of the 8 variables of the CDAI). The median CDAI of the patients enrolled in the study was 167.0 (range of 30.0 to 398.0) indicating that the overall severity of disease activity in this patient population, as measured by the CDAI, was mild.

Treatment with either the 5 mg/kg or 10 mg/kg cA2 treatment regimen produced decreases in the median CDAI of 70 to 100 points which were evident by the 2-week evaluation visit and then were well-sustained through the 18-week follow-up period. Decreases in the CDAI were not evident in the placebo group.

Perianal Disease Activity Index. A total of 85 patients had perianal disease at baseline (perianal fistulae, fissure or ulcerations). An improvement in the PDAI was seen as of week 2 in the cA2-treated patients. A further decrease (a 50.0% reduction compared to

baseline) was observed at week 6 and maintained through week 18. The placebo-treated patients showed a decrease of 1 point at week 2 and 3 points (a 33.3% reduction compared to baseline) at week 6. This reduction was maintained through week 14 with a slight increase toward baseline at week 18.

Steroid Tapering. Patients treated with oral corticosteroids had to keep their prescribed dosage stable through the week 6 evaluation visit. After this visit patients were allowed to taper their dosage using a predefined tapering schedule.

Thirty-two patients were treated with prednisone when enrolled in the study. In the cA2-treated patients a reduction is seen in the daily prednisone dosage of 25% to 33% with most reduction occurring in the 5 mg/kg dose group. The placebo patients showed no reduction at all.

Subgroup Analyses. To examine the consistency of the efficacy of cA2 treatment based on differences in demographic features, baseline disease characteristics and concomitant medications, odds ratios were evaluated for prespecified subgroups (see analytical plan) as well as for subgroups defined post-hoc. The odds ratio for a particular subgroup is the ratio of the odds that a cA2-treated patient achieves the primary endpoint (a $\geq$ 50% reduction from baseline in the number of draining fistulae observed for 2 consecutive evaluation visits [i.e., at least one month]) to the odds that a placebo-treated patient achieves the primary endpoint.

Men tended to show a greater treatment benefit than women (OR males = 13.3; OR females = 2.0) although the confidence intervals for these subgroups overlapped. It should be noted that the placebo response rate was twice as high in women compared to men. Consistent treatment benefit was observed for subgroups based on age and body weight. There were no differences in treatment benefit between the United States and European centers.

Effect of cA2 treatment in the closure of fistulae was observed regardless of concurrent therapies given. The odds ratio for response with cA2 was greater in patients not receiving either 6-MP/azathioprine, aminosalicylates, or oral steroids and/or immunosuppressants compared to patients taking one of these medications. There was no or minimal difference in the odds ratio between patients receiving or not receiving corticosteroids alone or taking antibiotics.

In addition, the odds ratio did not differ between patients with CDAI <150 (OR = 4.8) compared to those with CDAI >150 (OR = 4.9). There did not appear to be a difference in the odds ratio of response based upon the number of years that patients had had Crohn's disease: OR $\leq$ 5 years = 3.3, or 5-15 years = 7.3, and OR >15 years = 4.3.

3.4 FDA Analysis of Efficacy Data for Clinical Trial T20

3.4.1 Comments on the efficacy database:

1. The sponsor submitted photographs for each visit to document response of fistulae to cA2. All of the photographs were reviewed. It was difficult to corroborate the on-site clinical assessment of closure of fistula because of the amended definition from closure by visual inspection to lack of drainage with gentle compression. This amended definition interjects an element of subjectivity on the part of the examiner that can not be assessed by photographs.

   In addition, it is difficult to determine how the clinical investigator could assess closure by the amended definition for fistulae that drained into the vagina where there is generally some degree of mucous secretions. The source of the secretions in these patients may be difficult to discern. In these patients, assessment of the response depends entirely with the on-site examiner although review of the photographs can raise questions.

   For example, patient ——— who received 5 mg/kg of cA2, had a large single fistula draining within the vagina. Although the fistula responded visually on the photographs, the clinical reviewer could not determine the lack of drainage on week 2 and 6 as noted in the line listings. A visually open fistula could be seen at both visits. These two visits were the only time that the examiner recorded lack of drainage over the 18 week period thereby classifying the patient as a responder.

2. In addition to the vaginal fistula, there are doubts raised about data validity for 3 patients.

   ——— The patient had two perianal fistulae not accounted for in the line listings. These two fistulae could not be assessed for drainage by photograph but they were visually open. This patient was considered a responder because 4/4 fistula stopped draining. Despite these two additional fistula, he would remain classified as a responder even if these they remained open.

   ——— The patient had one perianal fistula that responded to 5 mg/kg cA2 by week 2 and is recorded in the line listings as closed except for week 10. On visual review of the photographs the fistula appears to be closed at week 10.

   ———. The perianal fistula was recorded as closed in the line listings at weeks 6 and 10 and open on the other examinations. However, visual review on the photographs raises doubts regarding closure at week 6 because the fistula appears to have some drainage.

3. No response was recorded for one or two visits over the 26 week study period in the line listings for three patients although photographs from those visits were provided. All of these patients were in the 5 mg/kg cohort.

- - week 2
- - week 2
- - weeks 22 and 26

Changes in classification of the patient response following review of the line listings and photographs. Although review of the patient photographs could not verify clinical response as defined by the protocol for most patients, there were 4 patients where the photographs clearly showed closed fistula at baseline or lack of response as recorded in the line listings. In addition, there was one patient where review of the clinical data recorded in the line listings indicate that the patient should be classified as a responder. It should be noted that 3 of the 5 patients were enrolled at site 5. As a result one placebo patient is reclassified as responder, one patient randomized to 5 mg/kg is reclassified as a nonresponder and three patients (two 5 mg/kg and one 10 mg/kg) are deleted from the efficacy analysis.

These patients are described below:

Placebo

- The patient had one eligible fistula that was recorded in the line listings as closed at weeks 10, 14, and 18. This patient received all three doses of study drug and did not experience an adverse event. This patient has been reclassified from a nonresponder to a responder.

5 mg/kg cA2

- The fistulae is recorded as open on all visits except at week 14 and 18 thereby categorizing this patient as a responder. Review of the photographs show that this patient had a huge "bedsore" type fistula at baseline that was open on all photographs of the clinic visits. The fistula did respond markedly but never closed. This patient was reclassified as a nonresponder.

- This patient had one fistula which was recorded as open at baseline and closed from week 2 until the end of the examination period. Review of the photographs showed no visual opening of the fistula and the skin was dry. This patient is considered ineligible for the study and is not included in the efficacy evaluation.

- Three open fistulae are recorded at baseline which all responded by week 2 and remained closed through the end of the study. Review of the photographs show no visual opening to any of these three fistula. This patient is removed from the efficacy evaluation.

10 mg/kg cA2

One open fistula is recorded at baseline that was closed on week 2 and on subsequent examinations. Review of the photographs showed no open fistula at baseline. This patient is removed from the efficacy evaluation.

3.4.2 FDA Analysis of the Efficacy Database.

Primary Endpoint. Table 27 shows the clinical response as defined by the primary endpoint (stoppage of draining fistulae as determined by gentle compression) at week 18 for patients after reclassification.

Table 27. Patients achieving the primary endpoint - T20

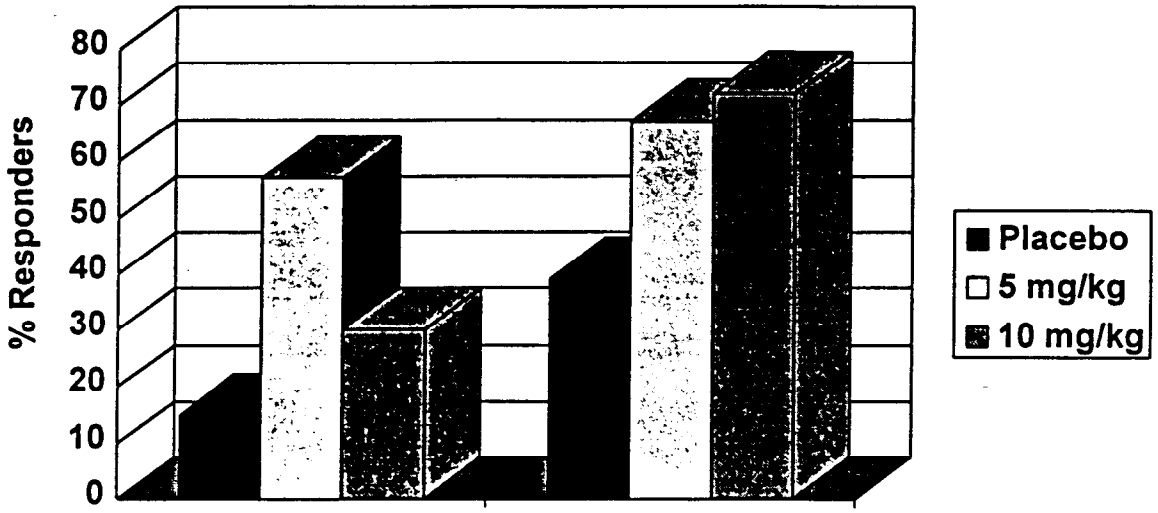
	Placebo (n=31)	5 mg/kg (n=29)	10 mg/mg (n=31)
Patients with ≥ 50% fistulae stopped draining	9 (29%)	18 (62%)	17 (54%)
p-value vs. placebo (two-sided Fisher's Exact Test		0.02	0.07

Treatment effect p-value (Mantel-Haenszel chi-squared test) = 0.043

The response in the 5 mg/kg cohort is higher than in the 10 mg/kg cohort but the difference is not significant. The difference between these two doses in the FDA's analysis is not as great as that reported by the sponsor (Table 23; see above), i.e., 68% vs. 56%, and also is not significant. Comparison between the results reported in Table 23 and 27 show that any change or inaccuracies in the assessment of clinical response in the treatment groups can markedly affect the analysis, given the small size of the cohorts. Also, the small size of the cohorts precludes a meaningful assessment of a dose response relationship.

Response according to single vs multiple fistulae. There were 42 patients with a single fistula and 52 patients with multiple fistulae enrolled into Study T20. Figure 3 compares the response rate for patients with single vs. multiple fistulae. The numerical data are shown in Table 28 below. A higher proportion of patients treated with cA2 responded by study definition compared to placebo regardless of whether they had a single or multiple fistulae.

Figure 3. Percent response by the number of fistulae at baseline.



Interestingly, review of the response for the different cohorts suggest that response to either placebo or cA2 is an "all or none" type, i.e., for a patient with more than one fistula, if one responds, the others seem to respond as well. For each cohort, there was only one partial responder, i.e., <50% of the fistula responded. This type of response may be due to the fact that these fistulae are interrelated such that they share the same source in the intestine.

Complete response. For patients with multiple fistulae, we evaluated the 100% response rate of fistulae that responded to treatment. However, the number are too few to made an adequate evaluation. Table 28 shows the 100% response of patients with single or multiple fistulae (response by patients with a single fistulae is 100% and is described simply as responder). The proportion of responding patients with multiple fistulae who closed all of their fistulae, were similar among the treatment arms, i.e., 4/7 (57%) in placebo, 7/10 (70%) treated with 5 mg/kg cA2, and 7/13 (56%) treated with 10 mg/kg cA2.

Table 28. Response by the number of fistulae at baseline (T20)

		Placebo (n=31)	5 mg/kg (n=29)	10 mg/kg (n=31)
1 fistula	responder	2	8	4
	non responder	11	6	9
>1 fistulae	responder			
	study definition	3	3	6
	100%	4	7	7
	non-responder	11	5	5

Maintenance of response. We analyzed the maintenance of response beyond the 18 week study period by calculating the proportion of responders who continued to have ≥50% of their fistula closed at the two evaluations following week 18 (Table 29). Response to placebo plus standard care was more durable compared to patients treated with cA2, who generally lost their response when treatment was stopped. This loss of response may indicate a lack of biologic activity internally, i.e., on the fistula canal, with this dose regimen.

Table 29.Maintenance of closure in responders before and after the 18 week study period.

Treatment	Patients with response	Response at 18 weeks	Response at 22 weeks	Response at 26 weeks
Placebo (n=31)	9 (29%)	8 (26%)	7 (23%)	6 (19%)
5 mg/kg (n=29)	18 (62%)	14 (48%)	7 (24%)	6 (21%)
10 mg/kg (n=31)	17 (55%)	13 (42%)	8 (26%)	3 (10%)

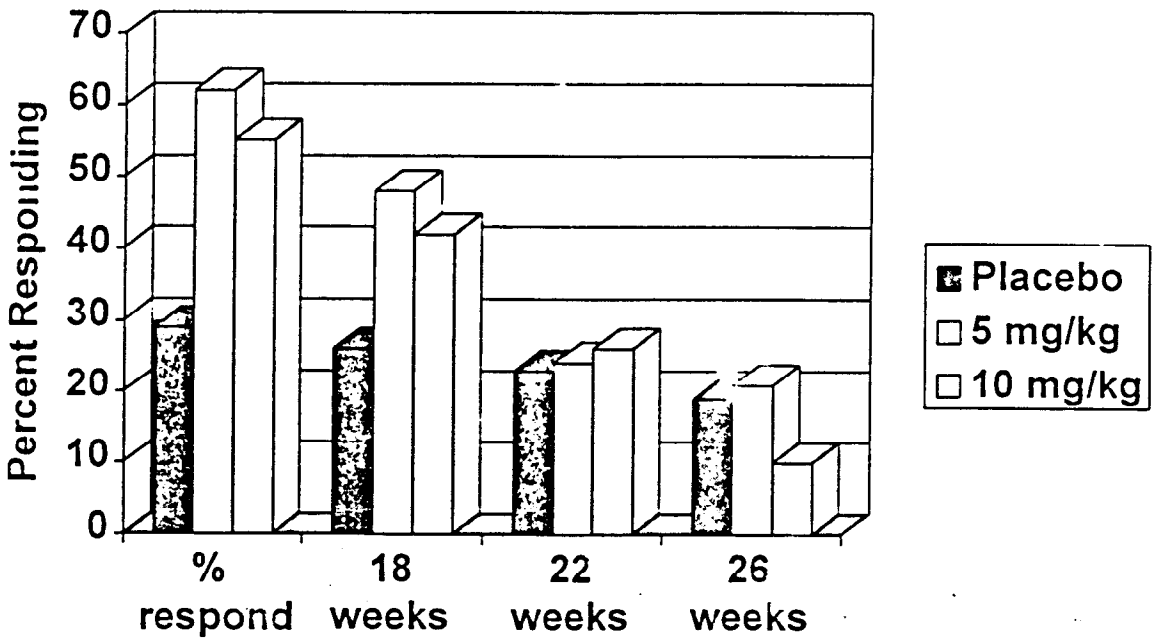
Duration of response. The number of weeks during which the patient maintained a response during the 26 week period was compared between placebo and the cA2 treatment groups (Table 30). The response period was analyzed by 4 week intervals starting from the first evaluation where the patient responded until the last evaluation during the 26 week evaluation period at which the patient continued to be in response. When no data were recorded a patient was censored and the preceding evaluation timepoint was used to calculate the duration of response. A response >24 weeks means that the patient responded from week 2 through week 26 of the study period. The cohorts were compared using a log-rank test and patients not responding had a duration of response equal to zero. There appeared to be no difference in response duration between cohorts. The log-rank test of the three-way comparison yielded a p-value of 0.92. Although there were a higher proportion of responders, overall, in the cA2 treatment groups, the proportions of patients who maintained a response through the 26 week evaluation period were similar among the three arms.

Table 30. Duration of response (T20)

Duration of response - weeks	Placebo (n=31)	5 mg/kg (n=29)	10 mg/kg (n=31)
0	22	11	14
(4-8]	0	5	2
(8-12]	1	2	3
(12-16]	3	4	4
(16-20]	0	3	1
(20-24]	4	2	5
>24	1	2	2
Total	9	18	17

Figure 4 shows the duration of respons at week 18, 22 and 26 for patients who were in response at the 18 week study period. At week 18, the proportion of patients treated with cA2 and in response by study definition was higher than patients treated with placebo. However, by week 12 this effect was lost.

Figure 4. Maintenance of Fistulae Closure for Responders in Clinical Trial T20.



Onset of response. A comparison between the cA2 and placebo cohorts is shown in Table 31. The majority of the patients in the cA2 treatment groups responded by week 2 whereas those randomized to placebo had their onset of response fairly evenly dispersed throughout the study period.

Table 31. Onset of response (T20)

Onset of Response	Placebo (n=31)	5 mg/kg (n=31)	10 mg/mg (n=32)
2 weeks	3	10	11
6 weeks	2	5	5
10 weeks	2	3	0
14 weeks	2	0	1
never responded	22	13	15

Per fistula analysis. The response was analyzed on a per fistula basis. The fistulae were categorized according to their age and fistulae ≤ 3 months were excluded. Table 32 shows the distribution of each fistulae by age and cohort. The greatest number of fistulae were in the 10 mg/kg cA2 cohort because one subject had 11 fistulae and another had 13.

Table 32. Age of fistula eligible for evaluation (T20)

	Placebo	5 mg/kg	10 mg/kg
>2 years	33 (44.6%)	24 (33.3%)	53 (58%)
1-2 years	10 (13.5%)	16 (22.2%)	19 (20.9%)
6-12 months	18 (24.3%)	8 (11.11%)	9 (10%)
3-6 months	5 (6%)	9 (13.2%)	7 (7.7%)
unknown	8 (10.8%)	11 (16.2%)	2 (2.2%)
Total	74	68	90

Table 33 shows the response of the fistulae to treatment with placebo or cA2 on a per fistulae analysis according to their duration prior to treatment. More fistulae responded to treatment with cA2 compared to placebo although the effect is less dramatic as in per patient analysis. Although the numbers are small, there appears to be difference in response to cA2 treatment in fistulae based upon their duration.

Table 33. Fistula that responded, categorized by duration of fistula (T20)

	Placebo	5 mg/kg cA2	10 mg/kg cA2
>2 yrs	12/33 (31.6%)	14/24 (58.3%)	24/53 (45%)
1-2 yrs	4/10 (40%)	12/16 (75%)	15/19 (79%)
6-12 months	7/18 (38.9%)	4/8 (50%)	6/9 (67%)
3-6 months	3/5 (60%)	5/9 (56%)	5/7 (71.4%)
<3 months	0/4 ---	3/3 (100%)	1/1 (100%)
unknown	4/8 (50%)	2/11 (18%)	2/2 (100%)
Total	78	75	92

Because of the small numbers per category when the fistulae are categorized by the length of their presence, we analyzed on a per fistula basis the number that closed regardless of their duration (Table 34). On a per fistulae basis, more fistula respond to either dose of cA2 compared to placebo but the response is much less than on a per patient basis (56% vs. 41%). In addition, the response to 5 mg/kg compared to 10 mg/kg is slightly less, 54.4% vs. 57.8%, which suggests that the dose response is nearly identical.

Table 34 also shows the number of fistulae that remained through the 26 weeks of evaluation. In this analysis, the percent of fistulae that remained closed in the placebo cohort is similar to the 5 mg/kg cA2 cohort (approximately 50%) while more (71%) of the fistulae closed with 10 mg/kg cA2.

Table 34. Per fistulae response for all fistulae (T20)

	Total fistula	Total responding	Remained closed
Placebo	74	30 (40.5%)	16 (53.3%)
5 mg/kg	68	37 (54.4%)	21 (50%)
10 mg/kg	90	52 (57.8%)	38 (71.3%)

We analyzed how many fistulae reopened prior to or at the week 18 evaluation and at subsequent evaluations (week 22 and 26) (Table 35). A similar percentage (25%) of fistulae reopened by the week 18 evaluation for the placebo and 5 mg/kg cohorts while less reopened (11.5%) in the 10 mg/kg cohort. More fistulae reopened after the week 18 evaluation in the 5 mg/kg cohort.

Table 35. Responding fistula that reopened before and after week 18 evaluation (T20)

		≤ 18 weeks		> 18 weeks	
	Total responding fistulae	reopened	week (mean)	reopened	week (mean)
Placebo	30	8 (26.7%)	15.6	6 (20%)	24.7
5 mg/kg	37	9 (24.3%)	14.0	12 (32.4%)	22.3
10 mg/kg	52	6 (11.5%)	14.7	9 (17.3%)	24.2

Development of new fistulae while on study drug. When the bowel wall is compromised the body attempts to contain the spread of the intestinal flora from entering the abdominal cavity by either forming an abscess or developing an entercutaneous fistula over time. T20 was not designed to obtain clinical data evaluating for effect of cA2 on fistula formation or for its effect on internal healing. MRI's were obtained at a few European sites but those results are not available for review. Analysis of the development of new fistulae while on study drug may indicate whether or not this dose regimen of cA2 had any biologic effect on the fistula internally.

Table 36 shows the number of patients in each cohort who developed new fistulae, the number of new fistulae that developed, the time at which they developed, and their location. Eight patients treated with placebo, 8 treated with 5 mg/kg cA2, and 1 patient treated with 10 mg/kg of cA2 developed new fistulae. New fistulae developed regardless of whether or not the patient was classified as a responder. Six of the nine patients treated with cA2 who developed new fistulae did so within the 18 week study period..

Results of this analysis and the greater proportion of patients treated with cA2 compared to placebo who developed abscess (see T20 safety review below) suggests that there is no internal healing of the fistula with the dose regimen evaluated.

Table 36. Development of new fistulae while on study drug (T20)
(A patient with an asterisk (*) was classified as a responder to therapy)

	PID	Number of new fistula	Time of occurrence (wks)	Location
Placebo	[redacted]	1	2	perianal
	[redacted]	3	2, 10, 22	perianal
	[redacted]	3	18	perianal
	[redacted]	3	6	perianal
	[redacted]	1	10	perianal
	[redacted]	1	26	abdominal
5 mg/kg cA2	[redacted]			
	[redacted]	1	6	perianal
	[redacted]	2	6 & 18	perianal
	[redacted]	1	2	perianal
	[redacted]	1	18	perianal
	[redacted]	1	10	perianal
	[redacted]	1	22	perianal
	[redacted]	2	22	abdominal
	[redacted]	1	26	perianal
10 mg/kg cA2				
	[redacted]	1	2	perianal

3.4.2.1 Conclusions on Analysis of Efficacy Database - T20.

1. Patients who received either 5 mg/kg or 10 mg/kg of cA2 were more likely to achieve closure of their fistulae (i.e., closure is defined as cessation of drainage from $\geq$ 50% of draining fistulae) than patients treated with placebo.

2. The onset of response in patients treated with cA2 occurred earlier compared to the onset of response in patients treated with placebo.

3. Response appeared to be lost when treatment with cA2 was stopped, while fistulae that responded to standard care tended to remain closed. Continued therapy with cA2 may be needed to maintain closure but no data are available to demonstrate this.

4. The endpoint of closure of fistulae as defined by no drainage with gentle compression is subjective. Some recorded responses may be inaccurate (should affect all study groups) or subject to unmasking effect. Because of the small number of subjects per cohort, minor changes in the numerator (number of responders) markedly influences the proportion of responders.

5. There are no clinical data evaluating the effect of cA2 upon internal healing. New fistulae can develop while on cA2 therapy. The loss of response when therapy is stopped and the occurrence of new fistulae suggest that, for some patients, ongoing disease activity exists preventing internal healing of fistulae over the 6 week study period.

6. It is unknown if additional therapy results in internal healing and maintenance of response after therapy cessation. Longer-term dosing data are needed to assess continued response to therapy, and MRI or other radiographic data will be required to determine the effect of cA2 upon the fistula canal internally.

7. Although cutaneous closure of fistulae represents benefit to the patient, analysis of the clinical data from T20 suggests that continued cA2 is needed to maintain response, but no data are presented to instruct physicians how to continue therapy.

3.4.3 Analysis of Safety Database from Clinical Trial T20.

Because of the small sample size for T20, analysis of the safety regarding the laboratory values (chemistry, hematology, etc.), anti-dsDNA antibody and HACA will be incorporated into the overall safety database analysis for all non-sepsis clinical trials evaluating cA2. This review will present the safety data for clinical events experienced by patients enrolled in T20.

Abscess formation. Patients enrolled in T20 experienced abscess formation. Closure of enterocutaneous fistulae may prevent drainage of the fecal flora from the inflamed bowel and lead to the formation of abscesses. Table 37 shows the distribution of patients who developed an abscess throughout the 26 week evaluation period. Except for one patient who was a partial responder (i.e., <50% of the fistulae closed), all patients who developed an abscess were responders to either cA2 or placebo.

Table 37. Abscess Development (T20)

	Placebo (n=31)	5 mg/kg (n=29)	10 mg/kg (n=31)	All cA2 Patients (n=60)
*Abscesses	1 (3.2%)	2 (6.9%)	5 (16.1%)	7 (11.7%)

The development of abscesses in the cA2 treated patients appears to develop more often after cessation of treatment. For adverse experiences reported beyond the week 18 examination, abscesses were reported in 4 (14.3%) patients treated with cA2 and in no patient treated with placebo. These abscesses included 2 perianal abscesses in patients treated with 10 mg/kg cA2, one abscess in the vulva of a patient treated with 5 mg/kg, and cutaneous skin abscesses in a patient treated with 5 mg/kg. Review of the clinical data submitted indicates that these abscesses developed in the area of the draining fistula.

Adverse events. All 94 patients enrolled in T20 were followed for safety. Table 38 reports adverse experiences according to the WHOART preferred term in order of decreasing frequency of events for events occurring in more than 1 cA2-treated patients. Across both cA2 treatment groups, the most frequently reported adverse experiences were headache (17.5%), abscess (11.1%), upper respiratory tract infection (9.5%), and fatigue (9.5%). Headache was reported by similar numbers of patients in each of the 3 treatment groups; abscess, upper respiratory tract infection, and fatigue were noted in more patients in the 10 mg/kg cA2 group than in either the placebo group or the 5 mg/kg cA2 group.

Table 38 Number of patients with any adverse experience by WHOART preferred term

	Placebo (n = 31)	5 mg/kg (n = 31)	10 mg/kg (n = 32)	All cA2-Treated Patients (n = 63)
Avg weeks of follow up	19.8	21.3	21.2	21.2
Pts with 1 or more adverse experience	20 (64.5%)	20 (64.5%)	27 (84.4%)	47 (74.6%)
WHOART preferred term				
Headache	7 (22.6%)	5 (16.1%)	6 (18.8%)	11 (17.5%)
Abscess	1 (3.2%)	2 (6.5%)	5 (15.6%)	7 (11.1%)
URI	2 (6.5%)	1 (3.2%)	5 (15.6%)	6 (9.5%)
Fatigue	2 (6.5%)	2 (6.5%)	4 (12.5%)	6 (9.5%)
Eczema	0 (0.0%)	2 (6.5%)	3 (9.4%)	5 (7.9%)
Nausea	0 (0.0%)	2 (6.5%)	3 (9.4%)	5 (7.9%)
Abdominal pain	0 (0.0%)	3 (9.7%)	1 (3.1%)	4 (6.3%)
Pain	3 (9.7%)	1 (3.2%)	3 (9.4%)	4 (6.3%)
Pruritus	0 (0.0%)	2 (6.5%)	1 (3.1%)	3 (4.8%)
Rash	3 (9.7%)	1 (3.2%)	2 (6.3%)	3 (4.8%)
Vomiting	0 (0.0%)	1 (3.2%)	2 (6.3%)	3 (4.8%)
Back pain	2 (6.5%)	1 (3.2%)	2 (6.3%)	3 (4.8%)
Chest pain	2 (6.5%)	1 (3.2%)	2 (6.3%)	3 (4.8%)
Fever	2 (6.5%)	1 (3.2%)	2 (6.3%)	3 (4.8%)
Acne	0 (0.0%)	1 (3.2%)	1 (3.1%)	2 (3.2%)
Dermatitis fungal	0 (0.0%)	0 (0.0%)	2 (6.3%)	2 (3.2%)
Rash maculopapular	0 (0.0%)	1 (3.2%)	1 (3.1%)	2 (3.2%)
Myalgia	2 (6.5%)	1 (3.2%)	1 (3.1%)	2 (3.2%)
Dizziness	3 (9.7%)	1 (3.2%)	1 (3.1%)	2 (3.2%)
Fecal incontinence	0 (0.0%)	1 (3.2%)	1 (3.1%)	2 (3.2%)
Flushing	1 (3.2%)	2 (6.5%)	0 (0.0%)	2 (3.2%)
Coughing	0 (0.0%)	1 (3.2%)	1 (3.1%)	2 (3.2%)
Pharyngitis	2 (6.5%)	0 (0.0%)	2 (6.3%)	2 (3.2%)
Urinary tract infection	1 (3.2%)	2 (6.5%)	0 (0.0%)	2 (3.2%)

Herpes simplex	0 (0.0%)	0 (0.0%)	2 (6.3%)	2 (3.2%)

Table 39 lists the adverse experiences reported beyond the week 18 evaluation. Abscess was the only adverse experience reported in more than 1 patient (all were cA2-treated). These abscesses included 2 perianal abscesses (18002 and 20001, 10 mg/kg), 1 abscess of the vulva (05001, 10 mg/kg) and small cutaneous skin abscesses (16001, 5 mg/kg).

Table 39 Number of patients with any adverse experience by WHOART preferred term from 18 weeks through 26 weeks (T20)

	Placebo (n= 31)	5 mg/kg (n=31)	10 mg/kg (n= 32)	All cA2-Treated Patients (n= 63)
Pts evaluated > 18 weeks	8	14	14	28
Avg weeks of follow-up	8.0	7.6	7.2	7.4
Pts with 1 or more adverse experience	2 (25.0%)	2 (14.3%)	5 (35.7%)	7 (25.0%)
WHOART preferred term				
Abscess	0 (0.0%)	1 (7.1%)	3 (21.4%)	4 (14.3%)
Eczema	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (3.6%)
Pharyngitis	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (3.6%)
Rhinitis	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (3.6%)
URI	1 (12.5%)	1 (7.1%)	0 (0.0%)	1 (3.6%)
Arthralgia	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Myalgia	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Discontinuation from the Study. One patient ( ) who received 10 mg/kg cA2 discontinued treatment (i.e., did not complete all 3 scheduled infusions) because of an adverse experience. This patient developed a serious adverse experience, pneumonia, 22 days after the second infusion that was assessed as possibly related to study agent and further study treatment was discontinued. One additional patient (placebo) discontinued from the trial after completion of all scheduled infusions due to an adverse experience. This patient reported 1 week after the third placebo infusion arthritis and fasciitis assessed as possibly related to study agent. Although a response was achieved at week 14 and 18, the patient did not return for the week 22 and 26 evaluation visits.

Infusion Reactions. Four cA2-treated patients (6.3%, 2 patients who received 5 mg/kg and 2 patients who received 10 mg/kg) and 2 placebo-treated patients (6.5%) had adverse experiences either during an infusion or within the 2 hours after the end of an infusion. These adverse experiences included dizziness and low temperature elevation in placebo patients (all during the first infusion) and dizziness, headache, chest pain, pain and flushing in cA2-treated patients. Only dizziness in a placebo patient (caused a temporary interruption of the infusion.

In addition, 10 cA2-treated patients and 1 placebo patient reported adverse experiences on the day of an infusion but with an unknown start time. These events included hot flushes and pruritis ani in a placebo patient and urinary tract infection, pruritis, abdominal pain, back pain, fatigue (2 cases), abnormal hepatic function, headache, nausea, rash, fecal incontinence, folliculitis and flu syndrome in cA2-treated patients. These events all occurred after infusion, except possibly for the hepatic function abnormality for which this information was not available.

Of the adverse experiences reported during an infusion or within the 2 hours after the end of infusion or on the day of an infusion without an onset time, 3 events were categorized as either pruritis or urticaria or as a cardiopulmonary disorder. Pruritis was reported in Patient [redacted] (5 mg/kg) and pruritis ani was reported in Patient [redacted] (placebo). The pruritis in Patient [redacted] had an onset on the day of the second infusion. The pruritis was mild and still present at the last evaluation at 18 weeks. One patient ([redacted] 10 mg/kg) reported a cardiovascular symptom, mild chest pain, during the first infusion. The infusion was not interrupted or discontinued and the chest pain resolved spontaneously within 1 hour. No adverse experiences were reported during the patient's second or third infusion. None of these events were serious; only one set of symptoms (abdominal pain, back pain and fatigue in Patient [redacted] in the 5 mg/kg group) was graded as severe.

Infections. A total of 10 patients (3 each in the placebo and 5 mg/kg dose groups and 4 in the 10 mg/kg dose group) developed 1 or more infections requiring oral or parenteral antibiotic treatment (the identification numbers of those patients are shown in Table 40). Two serious infections were reported; both occurred in the 10 mg/kg dose group. Patient [redacted] developed furunculosis of the right arm and of the right leg, and Patient [redacted] developed a pneumonia. Other infections included 4 urinary tract infections, vaginal infection, herpes simplex, hidradenitis, bronchitis and 2 upper respiratory tract infections. Two infections, hidradenitis and furunculosis, were still present and being treated at the last evaluation.

Table 40. Patients with infections requiring oral or parenteral antibiotics

Placebo	5 mg/kg	10 mg/kg
[redacted] (UTI, vaginitis)	02012 (UTI)	02002 (pneumonia, URI)
[redacted] (hidradenitis)	06004 (UTI)	02010 (herpes simplex)
[redacted] (cystitis)	22014 (bronchitis)	14001 (URI)
		16002 (furunculosis)

Serious Adverse Experiences. As shown in Table 41, 4 patients (12.5%) who received 10 mg/kg cA2 and 1 patient (3.2%) who received 5 mg/kg cA2 reported serious adverse experiences.

- Patient [redacted] 5 mg/kg) developed ureteral obstruction approximately 12 weeks after her third infusion. She presented with right-sided abdominal pain, and right

hydronephrosis was noted on ultrasound and CT scan. No etiology was found and she recovered with stent insertion.

- Patient [redacted] (10 mg/kg) developed chest pain and pneumonia approximately 3 weeks after her second infusion. The presentation was atypical in that there was no cough or sputum production, but a chest radiograph and computed tomography (CT) scan revealed an infiltrate, while a V/Q scan and pulmonary angiogram were normal. Her symptoms resolved within 1 week of institution of antibiotic therapy.

- Patient [redacted] (10 mg/kg) developed intestinal obstruction the day of the 18 week study visit (13 weeks after the third infusion). She was admitted and treated with intravenous antibiotics and discharged 4 days later.

- Patient [redacted] (10 mg/kg) presented with furunculosis (abscess) of the right arm and of the right leg approximately 2 months after the third infusion. The abscess on the right leg was 1 cm in diameter and was surrounded by a 10-cm diameter area of redness and induration. It was drained and the culture showed a staphylococcal species. After drainage the affected area remained sufficiently tender that the patient could not sit, resulting in an assessment of the adverse experience as severely disabling. Antibiotic therapy was continuing at the end of the last evaluation.

- Patient [redacted] (10 mg/kg) had an anal abscess drained 10 weeks after the third infusion.

The pneumonia (Patient [redacted]), furunculosis (Patient [redacted] and abscess (Patient [redacted], were assessed by the investigators as possibly or probably related to study agent.

Table 41. Number of patients with any serious adverse experience by WHOART preferred term (T20)

	Placebo (n= 31)	5 mg/kg (n= 31)	10 mg/kg (n= 32)	All cA2-Treated Patients (n= 63)
Avg weeks of follow up				
	19.8	21.3	21.2	21.2
Pts with 1 or more serious adverse experience				
	0 (0.0%)	1 (3.2%)	4 (12.5%)	5 (7.9%)
WHOART preferred term				
Furunculosis	0 (0.0%)	0 (0.0%)	1 (3.1%)	1 (1.6%)
Intestinal obstruction	0 (0.0%)	0 (0.0%)	1 (3.1%)	1 (1.6%)
Pneumonia	0 (0.0%)	0 (0.0%)	1 (3.1%)	1 (1.6%)
Chest pain	0 (0.0%)	0 (0.0%)	1 (3.1%)	1 (1.6%)
Abscess	0 (0.0%)	0 (0.0%)	1 (3.1%)	1 (1.6%)
Ureteral obstruction	0 (0.0%)	1 (3.2%)	0 (0.0%)	1 (1.6%)

3.4.3.1 Conclusions on Analysis of the Safety Database - T20.

1. Review of the safety database to clinical trial T20 indicates that patients with fistulizing Crohn's disease and who respond to treatment with cA2 are at greater risk for the development of abscesses.

(Note: Because of the small number of patients enrolled in T20, an overall review of safety issues are incorporated into Section 4.0)

4.0 Review of the Consolidated Safety Database

The safety database for this review includes the pooled safety databases for all clinical trials evaluating cA2 with the exclusion of [redacted] trials. The primary focus is on clinical trials evaluating cA2 in patients with Crohn's disease and [redacted]
Evaluation of this pooled database identifies 5 major safety concerns: deaths, malignancies, serious infections, infusion reaction, and formation of autoantibodies. In the majority of the studies cA2 is administered every 8 weeks because of its relatively long half-life. Consequently, any beneficial or adverse effects of cA2 upon the immune system can last for a number of weeks after a single injection. In order to address the concerns regarding deaths and malignancies, the sponsor has collected safety data on deaths and malignancies on patients for up to three years after the patient's completion of the clinical trial. The safety data evaluated for infection, infusion reactions and autoantibody formation are the data generated during the study period.

Description of the Follow-up Safety Database. A total of 627 patients have received cA2 either during a clinical trial or separately (compassionate use). Of these 627, 113 patients were enrolled into [redacted] trials and 523 patients were enrolled in [redacted] trials; 61 patients received only placebo and 462 patients received cA2. Because of the complicated medical course of patients with [redacted] these patients are excluded from the safety analysis. Table 42 depicts the follow-up safety data on the 523 patients enrolled into [redacted] trials. The majority of patients with Crohn's disease have been followed for up to 1 year while patients with [redacted] are in their second and third year of follow-up. The follow-up on patients enrolled in protocols other than Crohn's disease, [redacted] is not as complete as that for patients enrolled into Crohn's disease and

Table 42. Patients with follow-up safety data in [redacted]

	Crohn's disease		[redacted]
	Placebo	**cA2**	
Pts enrolled	34	202	
Pts with follow-up data	32 (94%)	183 (91%)	
Follow-up period			
6 mo.	17 (50%)	40 (20%)	
1 yr.	15 (44%)	113 (56%)	
2 yrs.	0	18 (9%)	
3 yrs.	0	12 (6%)	
Pts without follow-up data	2 (6%)	19 (9%)	

Number of cA2 infusions. Table 43 summarizes the exposure history for patients enrolled into r The data shown in this table excludes patients who received cA2 on a compassionate basis so the total numbers are slightly less than those in Table 42.

Table 43. Number of cA2 infusions for patients enrolled into non-sepsis trials

		Number of cA2 Infusions				
	Any cA2 infusion	**1**	**2**	**3**	**4**	**>5**
Crohn's disease	199	74	31	62	6	26

4.1 Deaths

There have been 13 deaths following completion of the clinical trials; two of these deaths occurred after the 3 year follow-up period. All deaths occurred in patients who received cA2. The deaths can be categorized into cardiac related (n=5), malignancy related (n=5), or pulmonary/infectious diseases related (n=3). Each is described separately below.

Cardiac related

- Coronary artery disease in a 59 year old man with ——— who received 2 infusions of cA2 (10 mg/kg) approximately 2 ¼ years prior to death.

- Myocardial infarction of the left ventricle in a 26 year old woman with Crohn's disease who received a single 20 mg/kg cA2 approximately 4 years prior to her death. Two years prior to her death she was hospitalized with a cytomegalovirus (CMV) pneumonia, associated with secondary bacterial infections and CMV vasculitis.

- Complications following coronary artery bypass surgery in a 73 year old male with ——— He received 5 infusions of 1 mg/kg of cA2 15 months prior to his surgery.

- Myocardial infarction in a 61 year old male with ——— and a history of prior MI and GI bleed. He received 5 infusions of 1 mg/kg of cA2 approximately 1 year prior to his death.

- Brain death following cardiac resuscitation in a 43 year old woman with ——— She received a single infusion each of 20 mg/kg and 10 mg/kg of cA2 approximately 16 months prior to her death.

Malignancy related

- B-cell, non-Hodgkin's lymphoma in a 48 year old man with a history of ——— and treatment with prednisone, methotrexate and azathioprine. He received 2 infusions 10 mg/kg cA2 at 2 week interval eighteen months prior to diagnosis by lymph node biopsy.

- Mixed epithelioid Hodgkin's lymphoma in a 60 year old man with history of ———. He was diagnosed 6.5 months after receiving one dose of 1 mg/kg cA2.

- B-cell lymphoma in a 61 year old male with a history of Crohn's disease and treatment with azathioprine. He was diagnosed 9.5 months after receiving one dose of open label 10 mg/kg cA2 as part of the open label segment of study T16.

- Poorly differentiated mucinous adenocarcinoma with lymph node involvement in a 76 year old man with ——— He received 2 infusion of cA2 (10 mg/kg) approximate 3 ½ years prior to his death.

- B-cell lymphoma in a 36 year old man with HIV/AIDS who received 2 infusion of 20 mg/kg cA2 approximately 9 months prior to diagnosis. The patient died approximately 2 years after his last infusion of cA2.

Pulmonary/Infectious Diseases related

- A 64 year old female with a history of ——— was treated with 7.5 mg/week methotrexate and 10 mg/kg cA2 for three doses. She was hospitalized with hypotension, decreased consciousness and staphylococcal pneumonia 14.5 weeks after the last dose of cA2. It is known that this patient had low but measurable levels of cA2 two weeks prior to the onset of pneumonia.

- Nonspecific pneumonitis in a 54 year old male with ——— who received an open-label dose of 3 mg/kg of cA2 approximately 20 months prior to his death. One year prior to his death, he was treated for a pulmonary empyema.

- *Pneumocystis carinii* pneumonia and CMV infection in a 52 year old male with Crohn's disease who received a single infusion of 1 mg/kg of cA2 approximately 5 months prior to his death.

4.2 Malignancies

A total of ten patients (2 patients with Crohn's disease, 7 patients with ——— , and 1 patient with HIV/AIDS) treated with cA2 developed malignancies: one developed metastatic breast cancer, one developed malignant melanoma, one patient developed thyroid carcinoma, four patients developed lymphoma, one patient developed gastric adenocarcinoma and one patient developed multiple myeloma. Five of these 10

patients died, and already have been described (see section 4.1). A description of these 5 patients is not provided again.

- A 56 year old woman with [redacted]s developed a pathologic fracture one week after receiving a single dose of 10 mg/kg cA2. She was diagnosed to have ductal breast cancer.

- A 52 year old man with [redacted] was diagnosed with superficial spreading melanoma 4.5 months after receiving 2 infusions of cA2 (5 mg/kg and 10 mg/kg).

- A 59 year old woman with [redacted] was diagnosed with multiple myeloma 17 months after the last of 5 infusions of 3 mg/kg cA2 in combination with 7.5 mg/week of methotrexate.

- A 65 year old woman with [redacted] was diagnosed with colon carcinoma approximately 41 months after an infusion of 1 mg/kg followed by an infusion of 3 mg/kg of cA2.

- A 40 year old woman with Crohn's disease who was diagnosed with thyroid carcinoma approximately 21 months after a single infusion of 5 mg/kg cA2. She had a history of hyperthyroidism and thyroid nodule documented prior to study enrollment. In addition to the thyroid cancer, she had a LEEP procedure of her cervix. Pathology of the cervix showed extensive endocervical microglandular hyperplasia and squamous metaplasia.

It is known that patients with Crohn's disease and rheumatoid arthritis are at a higher risk for the development of lymphomas compared to the general population. The reason for this increased risk is attributed either to immunological deficiencies associated with their underlying disease or from drugs used to control the disease. Because of this increased risk, a direct causal relationship between the diagnosis of lymphoma and treatment with cA2 cannot accurately be made with such a small patient exposure and safety database. However, the data are not inconsistent with the possibility that treatment with cA2 enhances the risk of malignancy, even when given over a relatively short period of time.

4.3 Infections

The number of patients experiencing infections requiring antibiotic therapy were reported twice as often in cA2-treated patients as in placebo-treated patients (21% compared to 11%). It should be noted that patients treated with cA2 were followed longer than patients treated with placebo which could affect the reported rates of infection. In cA2-treated patients, urinary tract infections, bronchitis, pharyngitis, moniliasis, coughing, upper respiratory tract infection, sinusitis, fever and herpes zoster were each reported by more than 1% of patients. In placebo-treated patients, urinary tract infections, coughing

and upper respiratory tract infections were the 3 most frequently reported infections, also reported by more than 1% of patients.

There were 7 cases of infections that resulted in discontinuation of treatment. These included infectious mononucleosis, hidradenitis, cholecystitis, pneumonia, sinusitus, bronchitis, and vaginitis. Four of these patients were enrolled into clinical trials evaluating Crohn's disease. The case of cholecystitis and pneumonia were considered serious infections.

Serious infections. Seventeen patients reported serious infections: 15 (3.3 %) received cA2 and 2 (1.8 %) received placebo. The serious infections in patients treated with placebo include a paravesicular abscess discovered at resection and a case of septic olecranon bursitis. The serious infections reported in the 15 cA2-treated patients are:

- 5 suspected cases of pneumonia;
- 2 cases of cellulitis;
- 1 infected central venous catheter,
- 1 multiple symptoms of unclear infectious etiology associated with B-cell lymphoma,
- 1 *Salmonella* sp. sepsis,
- 1 cholecystitis
- 1 endophthalmitis
- 1 postsurgical sepsis
- 1 bronchitis
- 1 furunculosis

All of these patients were on active treatment at the time of the development of their infection.

The development of 4 pulmonary infections are noteworthy because a pathogen was not isolated from any patient. Although the patients improved with treatment for pneumonia, there remains the concern that these cases represent an immunological pulmonary response to cA2 treatment rather than to an infectious agent. One of these four patient also had pleuritis and results of a pleural biopsy showed infiltrations with rheumatoid nodules.

4.4 Infusion reactions

A reaction to an infusion was defined as an adverse experience occurring during an infusion or within the 2 hours following the end of the infusion. Overall, 16% of patients who received a cA2 infusion had an adverse experience during the infusion period, while 6.5% of patients who received a placebo infusion had an adverse experience during the infusion period (Table 44). Percentages of patients receiving cA2 who had infusion reactions were similar in Crohn's disease protocols compared with non-Crohn's disease protocols (15.6% versus 16.1%). However, no patient in the non-Crohn's disease

protocols who received placebo had an adverse experience during a placebo infusion period, while 10.5% of Crohn's disease patients who received placebo did.

Table 44. Infusion reactions for [redacted] trials

	Crohn's disease	
	Placebo	**cA2**
Pts. treated	86	199
Pts with infusion reaction	9 (10.5%)	31 (16%)
No. infusions	227	477
Infusions with infusion reactions	9 (4%)	36 (7.5%)
nonspecific	6	29
dermatologic	0	0
cardiopulmonary (CP)	3	6
derm.& CP	0	1

For all protocols combined, headache, nausea, dizziness, flushing, pruritus, urticaria and chest pain were the adverse experiences most commonly reported during the infusion period, although the percentages of patients with these symptoms were small (all less than 5%). In Crohn's disease protocols, cA2-treated patients were most likely to report headache, nausea, dizziness, flushing, chest pain, hypotension and abdominal pain. Headache, pruritus, flushing, urticaria and fever were the adverse experiences that cA2-treated patients were most likely to report during the infusion period in non-Crohn's disease protocols.

Clinical reactions were either nonspecific or indicative of hypersensitivity. The hypersensitivity reactions could be categorized as either dermatologic or those involving cardiopulmonary symptoms.

Across all protocols, 453 patients received a total of 1207 cA2 infusions, with 16% of patients experiencing an infusion reaction. Fifty-eight infusion reactions (4.8% of cA2 infusions) were non-specific reactions, 14 (1.2% of cA2 infusions) were reactions with pruritus or urticaria, 18 (1.5% of cA2 infusions) were cardiopulmonary reactions, and 2 (0.2% of cA2 infusions) had symptoms of both pruritus/urticaria and cardiopulmonary disorders.

Nine infusion reactions (0.8% of all cA2 infusions) resulted in immediate discontinuation of study agent. Three of the reactions resulting in discontinuation of the cA2 infusion occurred in the T16 Crohn's disease trial, 3 occurred in the [redacted], and 1 occurred in each of the T07, T09, and T15/T17 [redacted]. Four of these reactions were assessed as serious (1 nonspecific reaction, 2 cardiopulmonary and 1 both dermatologic and cardiopulmonary). Three of the 4 serious infusion reactions

occurred in T16 (all resulting in discontinuation) and 1 occurred in T09 (did not result in discontinuation). For the 6 patients who experienced a nonserious infusion reaction that resulted in discontinuation of treatment, 2 had nonspecific symptoms, 1 had dermatological symptoms, and 3 had cardiopulmonary symptoms.

The following describes the four serious infusion reactions.

- A 35 year old man with Crohn's disease who developed lightheadedness, chest tightness and bronchospasm 30 minutes after start of the infusion (10 mg/kg) and "serious" hypotension (drop in BP from 140/95 to 90/45). Symptoms persisted for 20 minutes after the infusion was stopped; no treatment was administered. No further cA2 was given.

- A 48 year old woman with Crohn's disease who developed "serious" symptoms of hypotension, chest pain, dyspnea, and palpitations as well as symptoms of urticaria and flushing 10 minutes into the second infusion of cA2 (10 mg/kg). Symptoms resolved 7 minutes after the infusion was stopped; no treatment was administered. No further cA2 was given.

- A 34 year old woman with Crohn's disease who developed "serious" symptoms of dyspnea as well as symptoms of numbness in the left arm and lips; pain in the abdomen, hip, knee and back; flushing; nausea; and chills. These symptoms occurred 2 minutes into the infusion of 10 mg/kg of cA2. The patient had received 5 mg/kg during the initial stage of the trial (T16). Symptoms resolved within 2 hours; intravenous antihistamines and corticosteroids were administered. No further cA2 was given.

- A 65 year old woman with [redacted], who developed fever and an erythematous rash treated with an antihistamine. Due to drowsiness, the patients was hospitalized longer than specified by the protocol resulting in the classification of serious.

The following describes the 6 patients with non-serious reactions but who discontinued receiving additional doses of cA2.

- A 28 year old woman with [redacted], who received 2 infusion of 10 mg/k cA2 followed by one10 mg/kg cA2 infusion in extended treatment. The patient became flushed, complained of burning retrosternal sensation and lost consciousness 4 minutes after the start of the 3rd infusion. No pulse was detected. The patient recovered in 1 minute with the administration of subcutaneous adrenaline.

- A 34 year old woman with [redacted] who received 1 mg/kg of cA2 followed by 3 mg/kg cA2. Thirteen minutes into the second infusion, the patient complained of severe dyspnea, pressure in the head, nausea and vomiting. Oxygen

was administered, and the patient felt well 5 minutes after the infusion was discontinued.

- A 63 year old woman with [redacted] who was randomized to MTX and five infusions of 3 mg/kg of cA2. Ninety minutes into the 3rd infusion, the patient developed an urticarial rash; the infusion was stopped 30 minutes after the rash developed. The urticaria resolved within 2.5 hours of stopping the infusion; oral antihistamine was administered. Prior to the 4th infusion, the patient was given antihistamines and a test dose of cA2. Because no symptoms developed, the 4th infusion was begun. Forty minutes into this infusion, the patient developed pruritus and urticaria. The infusion was stopped and the patient given intramuscular antihistamines. The infusion was resumed slowly and completed within 3.5 hours. Her symptoms did not recur, and the urticaria resolved by 4 hours after the end of the infusion. However, urticaria recurred 10 days after the 4th infusion accompanied by a petechial rash which resolved without treatment within 6.5 weeks.

- A 39 year old woman with [redacted] who was randomized to MTX and five infusions of 1 mg/kg of cA2. Forty-five minutes into the 4th infusion the patient complained of chest tightness which resolved 5 minutes after the infusion was stopped. However, 45 minutes after reinitiation of the infusion, the patient complained of chest tightness and chills. Symptoms resolved 60 minutes after the infusion was stopped. The 4th infusion was resumed at a slow rate without development of symptoms. Before the 5th infusion, a test dose of cA2 was administered without difficulty. However. 45 minutes into the 5th infusion the patient complained of chest tightness, hills and tingling in the fingers. Symptoms resolved within 20 minutes after stopping the infusion. Another attempt to complete the infusion was aborted when the patient again developed symptoms.

- A 39 year old woman with [redacted] who was randomized to placebo (MTX) and five infusions of 10 mg/kg cA2. She developed hypotension during each of the first 3 infusions which responded to intravenous fluids and slowing of the infusion. The patient did not receive all of the 3rd infusion and was discontinued from the study.

- A 48 year old man with [redacted] who received 1 mg/kg of cA2 in one trial and was to receive 3 infusions of 10 mg/kg of cA2 in a subsequent trial. The patient experienced diaphoresis, flushing, fever, dizziness, transient amnesia, confusion and somnolence 15-30 minutes after completion of the 2nd infusion. Symptoms resolved within 2 hours after the end of the infusion. Approximately 40 minutes into the 4th infusion, the patient complained of dizziness and headache and became apathetic, amnesic, flushed and had involuntary hand movements. The symptoms resolved 40 minutes after the infusion was stopped; no treatment was given. The cA2 infusion was not resumed.

Infusion reaction by number of cA2 infusion. For all trials 7% of patients administered their first infusion of cA2 had an infusion reaction during the first infusion while 10.2% of patients experienced an infusion reaction during the second infusion of cA2. Subsequent infusions were associated without further increase in the incidence of infusion reactions. It should be noted that all 4 of the serious infusion reactions and 4 of the 9 infusion reactions resulting in discontinuation occurred with the second infusion of cA2. Three of the other reactions resulting in discontinuation occurred at the third infusion. These events suggests that serious infusion reactions to cA2 are more likely to occur with the second or third infusion.

Infusion reactions by human antichimeric antibody (HACA) response. Patients who were HACA-positive at any point during the trial were more likely than patients who were HACA-negative throughout the trial to experience a reaction to a cA2 infusion (36.3% vs 10.8%, respectively). More patients with hypersensitivity infusion reactions (dermatologic or cardiopulmonary symptoms) were observed among the HACA-positive patients. Three of the 4 serious infusion reactions occurred in HACA-positive patients (two patients with Crohn's disease), and 5 of the 9 patients with reactions resulting in premature discontinuation were HACA-positive.

4.5 Human Antichimeric Antibody Responses (HACA)

For all protocols conducted in patients with Crohn's disease or [redacted], 402 patients were treated with cA2 and 283 (70%) were evaluable for HACA determinations. Eighty patients (28% of evaluable patients) were HACA-positive, with 10% of those evaluable having positive titers of 1:10, 6% having titers of 1:20, and 12% having titers >1:20. The maximum titer observed was 1:20,480. In Crohn's disease protocols, 13% of evaluable patients were HACA-positive compared with 42% of evaluable patients in [redacted]. In addition, Crohn's disease patients who were HACA-positive tended to have lower titers than did [redacted]

Analysis of the number of cA2-treated patients with positive HACA responses by whether or not immunosuppressants were given at baseline suggest that patients on non-steroid immunosuppressants are less likely to develop positive HACA responses, particularly in patients with Crohn's disease (Table 45). Of the 25 Crohn's disease patients who received non-steroid immunosuppressants (mostly 6-mercaptopurine or azathioprine), none developed a positive HACA response.

Table 45. Development of HACA according to Immunosuppressant Therapy

Baseline Immunotherapy	Crohn's disease	[redacted]
Any		
n	99	
(+)HACA	10 (10%)	
Steroids only		
n	48	
(+)HACA	7 (15%)	
Other only		
n	25	
(+)HACA	0	
Steroids & Other		
n	26	
(+)HACA	3 (11.5%)	
None		
n	35	
(+)HACA	8 (23%)	

4.6 Autoantibodies: Antinuclear antibodies (ANA) and antibody against double-stranded DNA (anti-dsDNA)

Immune mechanisms have been implicated as 1 of the possible etiologies of disease for both Crohn's disease and [redacted], autoimmunity clearly plays a mechanistic role in [redacted]. Autoantibody profiles in early [redacted] of cA2 demonstrated a possible association between cA2 treatment and the induction of autoantibodies; subsequent studies in both [redacted] and Crohn's disease measured these antibodies following treatment. Therefore, autoantibody data are available from all of the [redacted] studies and from the 2 controlled trials of cA2 in patients with Crohn's disease (T16 and T20).

4.6.1 ANA status by treatment and underlying disease

The ANA status of cA2- and placebo-treated patients was similar at baseline. Of the 79 placebo-treated patients who were evaluated for ANA, 60 (76%) were ANA-negative at screening and 19 (24%) were ANA-positive. Of the 357 cA2-treated patients evaluated for ANA, 272 (76%) were ANA-negative at screening and 85 (24%) were ANA-positive. Few changes were seen in the ANA status of placebo-treated patients during the course of the trial, but approximately one-third (both in patients who were ANA-negative and those who were ANA-positive at baseline) of cA2-treated patients changed ANA status during the trial. These changes resulted in a net increase in the number of cA2-treated patients positive for ANA at the last evaluation (128 out of 357; 36%) compared with results

obtained at the beginning of the trial (85 out of 357; 24% positive at screening). These trends did not appear to be related to underlying disease, as similar trends were seen in both Crohn's disease and ———————————

4.6.2 Anti-dsDNA status by treatment and underlying disease

No placebo-treated patients who were evaluated for anti-dsDNA antibodies became anti-dsDNA antibody positive during the trial. One Crohn's disease patient treated with cA2 was positive at the screening evaluation and negative at the last evaluation and 1 ; patient treated with placebo was positive at the screening evaluation and negative at the last evaluation. Thirty-three cA2-treated patients (9%) became positive for anti-dsDNA at some point during the trial, with 13 (4%) remaining positive at the last evaluation. The rates of conversion to positive for anti-dsDNA antibodies were similar in Crohn's disease (9%)

Patients who developed signs of systemic lupus erythematosus (SLE). Although anti-dsDNA antibodies developed in approximately 9% of cA2-treated patients, only 2 patients (discussed below) developed clinical signs and symptoms of a lupus-like syndrome. Listings of adverse experiences were reviewed to look for the development of mild non-specific symptoms which might have pointed to a diagnosis of SLE in additional anti-dsDNA-positive patients. The only adverse experience that was frequently noted was arthritis (or arthralgia), but this was also seen in both cA2-treated patients who were anti-dsDNA negative and in placebo-treated patients, and can occur in patients with and Crohn's disease. Both of these patients had resolution of their symptoms with therapy.

Anti-dsDNA antibodies by immunosuppressant therapy at baseline. The number of cA2-treated patients who developed antibodies against dsDNA by whether or not immunosuppressants were being given at enrollment into the trial were compare. Treatment with an immunosuppressant of any type appeared to confer protection against development of anti-dsDNA antibodies, particularly in Crohn's disease patients. In Crohn's disease patients, 3.5% of patients (4 out of 115) on any immunosuppressant developed anti-dsDNA antibodies compared with 20.8% (10 out of 48 patients) not receiving an immunosuppressant. In all protocols combined, 6.3% (16 out of 253 patients) of patients on any immunosuppressant developed anti-dsDNA antibodies compared with 17 out of 111, or 15.3% not receiving any immunosuppressant.

Concomitant medications were reviewed to look for an association between treatment with sulfasalazine products and development of anti-dsDNA antibodies. Two patients out of 11 on sulfasalazine derivatives were anti-dsDNA positive compared with 12 out of 152 patients not on a sulfasalazine product.

Anti-dsDNA antibodies by baseline ANA status. Patients who were positive for ANA at study entry were more likely to develop anti-dsDNA antibodies following treatment with cA2. Crohn's disease patients were approximately 2 times more likely to develop

anti-dsDNA antibodies and rheumatoid arthritis patients 4 times more likely, if they were ANA-positive at study entry.

4.6.3 Summary of autoantibodies

Approximately 1/3 of cA2-treated patients changed ANA status from negative to positive during the trials. Similar trends were seen in patients with both Crohn's disease and

Thirty-one (8.7%) of cA2-treated patients because positive for anti-dsDNA during the trial with 11 (31%) remaining positive at the last evaluation. Similar trends were seen in both Crohn's disease and .

Two patients developed clinical signs of lupus. One was a patient who developed dyspnea and pericarditis with resolution of her symptoms within 6 to 8 weeks of initiation of treatment with oral steroids. The other was a Crohn's disease patient who developed lupus arthritis, which also responded to corticosteroids and symptoms resolved within 6 months after the last cA2 infusion.

Possible factors influencing the development of anti-dsDNA antibodies were explored. No clear association of total cA2 exposure with the development of anti-dsDNA antibodies was noted. However, some patterns were detected for Crohn's disease patients: (1) baseline therapy with an immunosuppressant of any type appeared to confer protection against development of anti-dsDNA antibodies; (2) Crohn's disease patients who were ANA-positive before therapy were approximately 2 times more likely to develop anti-dsDNA antibodies while patients 4 times more likely to develop anti-dsDNA antibodies.

4.7 Laboratory and vital signs evaluation

Hematology and clinical chemistry measurements and vital signs measurements were reviewed to look for potential links between changes in these parameters and cA2 treatment. Review of urinalysis results in each of the individual clinical trials did not uncover any remarkable findings.

4.7.1 Hematology

Changes in hematologic parameters were remarkable only for changes in white blood cell parameters, for which increases in total WBC count were noted more frequently among cA2-treated than placebo-treated patients, predominantly in non-Crohn's disease patients. In Crohn's disease, 12.5% of placebo-treated patients had an increase in WBC count and 1.8% had a decrease, compared with increases in 15.6% of cA2-treated patients and decreases in 6.5% of patients. In non-Crohn's disease, 8.3% of placebo-treated patients had an increase and 4.2% had a decrease; for cA2-treated patients, 16.1% had an increase and 7.1% had a decrease. Changes for individual patients were generally mild and

transient, and no general or dose-related trends in changes in WBC count were noted. Clear associations with clinical events were not found. A shift in WBC count differentials was also noted, with decreases in neutrophil counts and increases in lymphocyte count, perhaps indicating a possible decrease in systemic inflammation in cA2-treated patients.

4.7.2 Clinical Chemistry

Analysis of clinical chemistry laboratory evaluations were noteworthy for the changes seen in creatinine and in liver function parameters. Increases were seen in creatinine in 5.1% of cA2-treated patients, but were not noted in placebo-treated patients. More of these increases were seen in Crohn's disease cA2-treated patients than in non-Crohn's disease cA2-treated patients, but the changes were mild (always to an absolute value of less than 2 mg/dl) and transient, without associated clinical events.

For the laboratory assessments of SGOT/AST and SGPT/ALT, increases occurred more frequently in cA2-treated patients than in placebo-treated patients. The most remarkable differences were noted in SGPT/ALT, for which 28.3% of cA2-treated patients had an increase (offset by decreases in 5.3% of patients) compared with 11.5% of placebo-treated patients (offset by decreases in 10.6% of patients). Increases in SGOT/AST were noted in 21.0% of cA2-treated patients (offset by decreases in 3.9% of patients) and in 15.4% of placebo-treated patients (offset by decreases in 6.7% of patients). There were no general or dose-related trends in changes in these liver function parameters and the changes were generally mild and transient and frequently normalized while treatment with cA2 was ongoing. No associated clinical symptoms were noted.

4.7.3 Vital Signs

Changes in vital signs measurements were noted primarily in systolic blood pressure during the infusion periods. Systolic blood pressure decreased during at least 1infusion by a factor of 10% and outside the normal range in 24.4% of all cA2-treated patients compared with 11.5% of all placebo-treated patients. This difference was slightly more pronounced in Crohn's disease patients (32.8% compared with 14.3%) than in non-Crohn's disease patients (16.6% compared with 8.3%). Changes were transient, rarely associated with a decrease in diastolic blood pressure or pulse and occurred more commonly in patients with low baseline systolic blood pressure. Changes in diastolic blood pressure were balanced between increases and decreases and no notable trends were observed for pulse or body temperature.

4.8 Conclusions on Review of Summary Safety Database

1. Given the chronicity of both Crohn's disease and [redacted], the combined safety database is limited. Assessments of the safety of cA2 are, therefore, somewhat problematic.

2. The clinical trials done to date are phase 2 clinical trials involving 2 to 3 different dose regimens of cA2. The number of patients who have received 5 mg/kg of cA2 (the recommended dose) to assess regarding safety is relatively small. The number of patients who received only placebo are too small to be of much use as a comparator. In addition, there is limited information on the safety of retreatment, which is probably how this medicine will be used clinically. In summary, the safety database is small and assessments of the overall risk/benefit ratio are, therefore, somewhat compromised.

3. All of the deaths and malignancies reported in the follow-up safety database occurred in patients who received cA2. However, an association between treatment with cA2 and these adverse events cannot be accurately determined because of the discrepancy between the numbers of patients exposed to cA2 compared to placebo. However, an association cannot be ruled out. Concern remains regarding the potential increased risk of lymphoma with cA2 therapy.

4. There is an association between treatment with cA2 and the occurrence of infections. Some of these infections are quite serious. The number of events is too small to determine what interplay, if any, exists among the use of concomitant immunotherapy, the underlying disease process, and the adjunct administration of any dose of cA2.

5. There appears to be an association between the development of HACA and occurrence of infusion reaction. Most of the infusion reactions occurred with the second infusion of cA2, a time when appearance of HACA should first occur. In addition, the use of immunosuppressant therapy appears to decrease the risk of HACA formation and, perhaps, the occurrence of infusion reactions.

6. There appears to be an association between the administration of cA2 and the development of autoantibodies. Two patients developed symptoms of drug-induced lupus.

5.0 Summary Conclusions on the Review of the Safety and Efficacy Data

The sponsor has presented phase 2 clinical data results to support licensing of a potent, novel immunomodulating agent for the management of patients with Crohn's disease, a chronic debilitating disease. Although the overall incidence of the disease is relatively low in the developed world, there are a sufficient number of patients to allow adequate, well controlled and adequately powered clinical trials to be conducted. (The Crohn's disease Foundation states that there are 200,000 children in the USA affected by Crohn's disease.) The number of patients with moderate to severe disease who have received the proposed dose of 5 m/kg of cA2 is very low (n=28) and no patients have received chronic retreatment with 5 mg/kg every 8 weeks as proposed in the original submission. The affects of a single dose are approximately 12 - 16 weeks, compatible with the half-life of the compound. [redacted]. For patients with fistula, although the majority of patients experienced stoppage of drainage in two weeks, there are no data on internal healing of the fistula canal. Once cA2 was stopped the effect of therapy was lost. In summary, there are inadequate data to support the long term benefit of cA2 in patients with either fistulizing or moderate/severe disease.

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