SUMMARY OF SAFETY AND EFFECTIVENESS DATA
for a SUPPLEMENTAL PREMARKET APPROVAL APPLICATION

I. GENERAL INFORMATION

Device Generic Name: Extracorporeal Immunoadsorption Protein A Column

Device Trade Name: Prosorba® column

Applicant's Name and Address:

Cypress Bioscience, Inc.
4350 Executive Drive, Suite 325
San Diego, CA 92121

Premarket Approval (PMA) Supplemental Application Number: P850020/S11

Date of Panel Recommendation: October 29, 1998

Date of Good Manufacturing Practices (GMP) Inspection:
The last two GMP inspections were conducted during the periods of March 25 to April 7, 1997 and March 12 to March 19, 1998. No violations were noted.

Date of Notice of Approval to Applicant: MAR 15 1999

This device was originally approved on December 23, 1987, for the limited indication for use in the therapeutic removal of immunoglobulin G (IgG) and IgG-containing circulating immune complexes from plasma in patients with idiopathic thrombocytopenic purpura (ITP) having platelet counts less than 100,000 mm^3. The sponsor submitted this supplement to expand the clinical indications. The updated clinical data to support the expanded clinical indication for use in the therapeutic reduction of the signs and symptoms of rheumatoid arthritis (RA) is provided in this summary. The preclinical test data were presented in the original PMA application. For more information on the data which supported the original indication, the summary of safety and effectiveness data for the original PMA should be referenced. Written requests for copies of the summary of safety and effectiveness data can be obtained from the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD, 20852 under Docket 88M-0019.

II. INDICATIONS FOR USE

The Prosorba® column is indicated for use in the therapeutic removal of immunoglobulin G (IgG) and IgG-containing circulating immune complexes from plasma in patients with idiopathic thrombocytopenic purpura (ITP) having platelet counts less than 100,000 mm^3.

The Prosorba® column is indicated for use in the therapeutic reduction of the signs and symptoms of moderate to severe rheumatoid arthritis (RA) in adult patients with long-standing disease who have failed or are intolerant to disease-modifying anti-rheumatic drugs (DMARDS).

III. DEVICE DESCRIPTION

The Prosorba® column contains Protein A covalently bound to an inert silica matrix. Protein A is a 42 kD molecular weight protein synthesized by certain strains of *Staphylococcus aureus*. Protein A binds immunoglobulin G (IgG) and IgG bound to an antigen, i.e., circulating immune complex, and to a lesser extent, IgM and IgA. Each column contains 123 $\pm$ 2 g of the Protein A/silica matrix and is capable of binding 557 mg of IgG when fully saturated. The column housing is composed of polycarbonate with luer-type polycarbonate connectors. The column is 6 inches long and 3 inches in diameter and has a priming volume of 300 ml.

The Prosorba® column is designed to process plasma, and must be used in conjunction with standard plasmapheresis equipment. After passage through the Prosorba® column, the treated plasma is returned to the patient.

IV. CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

The use of the Prosorba® column is contraindicated in patients who:

- Are currently receiving angiotensin-converting-enzyme (ACE) inhibitor medications;
- Cannot tolerate therapeutic apheresis procedures and have demonstrated a prior hypersensitivity associated with therapeutic apheresis;
- Exhibit evidence of, or have a history of, hypercoagulability;
- Have pre-existing abnormalities of the coagulation system in which activation of the coagulation system may precipitate a thrombotic event or a recent history of thromboembolic events.

The Warnings and Precautions can be found in the Professional Labeling.

V. ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The most common adverse effects that were observed during clinical use of the Prosorba® column in RA patients included joint pain, fatigue, joint swelling, hypotension, nausea, abdominal pain, flushing, paresthesia, headache, hematoma, dizziness, sore throat, rash, diarrhea, edema, hypertension, generalized pain, chills, dry mouth, nervousness, anemia, chest pain, respiratory difficulties, fever, muscle tightness, itching/hives, infection, and twitching. Sepsis was also observed.

Other potential complications which were not seen during clinical evaluation include blood or plasma loss from leaks within the apheresis equipment, hemolysis secondary to mechanical stresses, and significant fluid balance mismanagement.

VI. ALTERNATE PRACTICES AND PROCEDURES

RA has been historically managed in a "therapeutic pyramid" approach whereby initial therapy consists of anti-inflammatories, including corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs). Failure of these therapies leads to the administration of one or more DMARDs, including methotrexate, hydroxychloroquine and gold. Current practice trends are to

initiate DMARD therapy earlier in the course of treatment. Therapy with the Prosorba® column is only indicated for patients who have failed or are intolerant to DMARDs.

VII. MARKETING HISTORY

The Prosorba® column has been marketed with an indication for treatment of ITP in the United States since 1987. The product is approved and sold in Canada, Spain, Taiwan, Germany, Mexico, Australia and Great Britain for indications other than treatment of RA. The Prosorba® column has never been withdrawn from any market for reasons of safety or effectiveness.

VIII. SUMMARY OF PRE-CLINICAL STUDIES

A summary of the pre-clinical studies is provided in the Summary of Safety and Effectiveness Data for the original PMA. A copy can be obtained from the Dockets Management Branch at the address given above.

IX. SUMMARY OF CLINICAL STUDIES

A. ITP Study

A summary of the clinical study to support the ITP indication is provided in the Summary of Safety and Effectiveness Data for the original PMA. A copy can be obtained from the Dockets Management Branch at the address given above.

B. Preliminary RA Studies

Independent, Physician-Sponsored Feasibility Study[1]

The objective of this physician-sponsored study was to evaluate the safety and effectiveness of extracorporeal immunoadsorption with the Prosorba® column in the treatment of RA. Eleven patients with refractory RA were enrolled in this open-label, prospective trial of 24 weeks duration. Nine patients received 15 treatments over a 12 week period, 1 patient received 15 treatments over a 15 week period, and 1 patient received 12 treatments over a 9 week period. The composite criteria of Paulus[2] were used to assess the clinical condition of these patients at all time points. This criteria includes ESR, morning stiffness time, number of tender joints, number of swollen joints, physician assessment of disease activity and patient assessment of disease activity. Using the Paulus criteria, 9 patients showed $\geq$ 50% improvement at week 13, while 4 and 2 patients showed $\geq$ 50% and $\geq$ 20% improvement, respectively, at week 24.

RA Pilot Study #1

This single-arm study was conducted at 3 institutions with 14 patients. Eligible patients were treated at a frequency of two immunoadsorption treatments per week for 3 weeks followed by one treatment per week for 9 additional weeks, for a total of 15 treatments over 3 months. The average duration of disease for the patients enrolled was 11.8 years. Of the 14 patients enrolled, only 6 patients completed the full protocol. Of these six patients, three showed $\geq$ 50% improvement in Paulus criteria and 1 showed a 20% improvement.

RA Pilot Study #2

This was an uncontrolled, open-label study of 15 patients at three investigational sites. Patients who had failed to respond to two or more DMARDs were washed out of DMARDs for 1 to 3 months prior to enrollment. Of the 15 patients enrolled, there were four males and 11 females with a mean age of 50.4 $\pm$ 9.9 years and a mean duration of disease of 10.9 $\pm$ 6.8 years. The patients had an average of 27.8 $\pm$ 12 tender joints and 18.5 $\pm$12.4 swollen joints. They had failed an average of 3.7 $\pm$ 2 DMARDs.

Patients were treated with the Prosorba® column once per week for twelve weeks. At each session, approximately 1250 ml of plasma was treated at a flow rate of 10-20 ml/min. Clinical evaluations were performed at study enrollment and monthly throughout the treatment phase. Patients were followed for 12 weeks following the last treatment, and assessments were performed at weeks 1,2, 4, 8 and 12 following the last treatment.

The improvement in Paulus criteria at the 16 week post-enrollment time point (4 weeks after the last treatment) was used as the primary endpoint, although as noted above, assessments were made at other time points.

Four weeks after the last treatment, 9 of the 15 patients showed > 20% improvement and 7 of the 15 patients showed > 50% improvement in the Paulus criteria. An analysis of the changes in the means of each of the six indices used in the Paulus criteria are shown in Table 1. Statistically significant improvements were seen at weeks 16, 20 and 24 in painful joint count, swollen joint count, ESR, patient global assessment and physician global assessment.

The most common adverse effect that was observed was an arthritic-flare type reaction characterized by increased joint pain shortly after completion of a procedure. This was observed in 27% of the procedures. Other adverse effects that were observed include fatigue (9.3%), tingling/numbness (6.7%) and chills (5.6%). After the last treatment, significant decreases in hemoglobin and hematocrit were observed.

Table 1. Evaluation of All Patients Using An Intent To Treat Analysis- US Pilot Study

Parameter	Baseline Value	Month 4	Decrease	p Value	Month 5	Decrease	p Value	Month 6	Decrease	p Value
Painful Joint Count	27.80	11.53	58.51%	0.001	9.07	67.39%	0.0001	11.27	59.47%	0.001
Swollen Joint Count	18.47	9.07	50.90%	0.05	7.53	59.21%	0.01	7.47	59.57%	0.01
Patient Assessment of Disease Activity	2.67	1.67	37.50%	0.05	1.40	47.50%	0.01	1.80	32.50%	0.01

Parameter	Baseline Value	Month 4	Decrease	p Value	Month 5	Decrease	p Value	Month 6	Decrease	p Value
Physician Assessment of Disease Activity	3.00	1.67	44.44%	0.01	1.53	48.89%	0.01	1.73	42.22%	0.01
Morning Stiffness	406	328	19.29%	NS*	242	40.31%	NS*	358	11.74%	NS*
ESR	46.7	33.5	28.14%	0.05	28.3	39.29%	0.01	34.7	25.71%	0.05

*Not significant

C. RA Pivotal Study

This study was designed as a Phase III, prospective, multi-center, randomized, sham-controlled, double-blinded clinical study of patients with severe and active RA who had failed one or more DMARDs. The study randomized 109 patients at twelve sites. The difference between active and sham treatment was distinguished by whether plasma was passed through the Prosorba® column. All other aspects of the plasmapheresis treatment were the same for both groups.

The objective of the study was to evaluate the safety and effectiveness of the Prosorba® column in the treatment of patients with RA. Upon enrollment, patients were treated once per week for 12 weeks. Patients were evaluated for disease activity at regularly scheduled intervals during the 12 weeks of treatment and for at least 12 weeks after the last treatment. Assessments were performed using the American College of Rheumatology (ACR) core set of criteria for measuring disease activity[3]. The ACR criteria consists of:

- The number of tender joints (i.e., exhibit tenderness on pressure or pain on passive motion);
- The number of swollen joints;
- The patient's assessment of pain as measured with a visual analog scale;
- The patient's global assessment of disease activity as measured with a visual analog scale;
- The physician's global assessment of disease activity as measured with a visual analog scale;
- The patient's assessment of physical function as measured with the Health Assessment Questionnaire (HAQ); and
- Determination of C-reactive protein level.

The primary effectiveness outcome measurement was a comparison of the average of two assessments performed at weeks 19 and 20 (7 and 8 weeks after the last treatment) with the original baseline value (an average of three assessments performed weekly prior to entry into the study). A response to treatment was defined as an improvement of $\geq$20% for the tender joint count, swollen joint count and 3 of the 5 additional criteria. (This definition coincides with the ACR 1995 Primary Definition of Improvement in Rheumatoid Arthritis.[4])

All patients entering the trial were required to discontinue DMARD therapy for one month prior to enrollment in the case of methotrexate and sulfasalazine, and three months in the case of all other DMARDs.

Inclusion criteria

The inclusion criteria for the study were:

- Age > 18 years;
- Negative pregnancy test;
- Patients must have rheumatoid arthritis, according to American Rheumatism Association (ARA) criteria[5] of more than 12 months duration, onset after age 16, incompletely controlled with conventional therapy;
- Patients must have failed an adequate clinical course of <u>two</u> of the following agents: gold, penicillamine, azathioprine, hydroxychloroquine or sulfasalazine; or the patient must have failed <u>one</u> adequate clinical course of methotrexate. Failure is defined as a worsening of symptoms or a flare of disease;
  <u>or</u>
  Patients must demonstrate intolerance of each of the above agents (i.e., gold, penicillamine, azathioprine, hydroxychloroquine, sulfasalazine or methotrexate). Intolerance is defined as experiencing side effects necessitating discontinuation of the drug;
- Patients must have 20 or more tender joints;
- Patients must have 10 or more swollen joints (not just bony overgrowth) observed by a physician and considered capable of responding to therapy;
- Patients must have a Patient's Global Assessment of disease activity of at least 5 cm toward "Very Poor" on a 10 cm visual analog scale;
- Patients must have a Physician's Global Assessment of disease activity of at least 5 cm toward "Very Poor" on a 10 cm visual analog scale;
- Patients must exhibit morning stiffness of at least 60 minutes duration;
- Patients must be in RA functional class[6] II or III;
- Patients must be on a stable dose of non-steroidal anti-inflammatory drugs (NSAIDs) and/or corticosteroid not to exceed the equivalent of 10.0 mg/day of prednisone. The corticosteroid dose must have been given for at least 30 days prior to entry and may not be changed during the study;
- Patients must have adequate peripheral venous access to allow completion of the full treatment protocol;
- Patients must give informed consent.

Exclusion Criteria

The exclusion criteria were:

- Patients having any medical condition which makes extracorporeal immunoadsorption with a Protein A column medically contraindicated (e.g., intolerance of therapeutic apheresis, hypersensitivity associated with a therapeutic apheresis, inability to obtain adequate anticoagulation, pre-existing abnormalities of the coagulation system, concurrent use of ACE inhibitor medications);
- Patients with myocardial infarction within the past 6 months, active cardiac disease (American Heart Association class 3 or 4), congestive heart failure or prosthetic valve disease;
- Patients with life-threatening pulmonary dysfunction;
- Patients with hepatitis B or active liver disease (levels of SGOT [AST] and alkaline phosphatase > 2x the upper limit of the normal range for the laboratory performing the test);
- Patients with renal impairment (creatinine > 130% of the upper limit of the normal range for the laboratory performing the test);

- Patients with hematocrit < 27;
- Patients with hemoglobin < 9.0;
- Patients with any of the ARA exclusion criteria for RA;
- Patients with other forms of arthritis (except osteoarthritis);
- Patients in RA functional class I or IV;
- Patients who have received therapy with gold, penicillamine, hydroxychloroquine or azathioprine within 3 months prior to entry into the study or with methotrexate or sulfasalazine within 30 days prior to entry into the study;
- Patients who are receiving concomitant treatment with a DMARD or cytotoxic agent;
- Patients treated with other investigational therapy concurrently or within 30 days prior to entry into the study;
- Patients treated with other investigational disease modifying anti-rheumatic drugs within 90 days prior to entry into the study;
- Patients who have received cyclosporin A, cyclophosphamide or monoclonal antibodies within 90 days prior to entry into the study;
- Patients who have received any anti-CD4 or T-cell directed therapy in the last six months or patients who previously received anti-CD4 or T-cell directed therapy and who do not currently have normal CD4 counts and/or immune function;
- Patients with active malignancy within 5 years prior to entry into the study (except for patients with non-metastatic skin cancer which has been treated and has not required further treatment for at least 12 months prior to entry);
- Patients with a systemic infection;
- Patients who have had recent (within 6 weeks) major surgery;
- Patients undergoing concomitant anticoagulant therapy;
- Patients with active peptic ulcer or inflammatory bowel disease;
- Patients with known hypersensitivity to *Staphylococcal* products;
- Patients with positive HIV test;
- Patients who are abusing drugs or alcohol (determined by standard urine analysis at the discretion of the investigator);
- Patients who have received therapy with other agents acknowledged to have activity in RA (e.g., Minocycline) within 30 days of entry.

Of the 109 patients who were randomized, 52 were assigned to the Prosorba® group, 47 to the sham group and 10 patients were randomized but were switched to an open label study, discussed in more detail in the sections that follow. Table 2 provides demographic information on the 99 patients who entered the sham-controlled pivotal trial.

Table 2 - Demographic Data and comparison between treatment groups for RA pivotal study.

Characteristic	Sham group Mean ± SD	Prosorba® group Mean ± SD	P value Prosorba® vs sham	Study overall
Age (yrs)	52.4 ± 10.8	53.0 ± 10.4	0.7838	52.7 ± 10.6
Gender (female %)	71.1	82.4	0.0900	77.1
Prior disease duration (yrs)	17.4 ± 10.3	14.6 ± 10.0	0.1732	16.0 ± 10.2
Prior disease duration (yrs)(min/max)	2.4 - 42.6	1.7 - 50.6		1.7 - 50.6
Percent RF	94	90		91
Class III Stage (%)	48.9	38.5	0.3170	43.4
Prior Methotrexate Use (%)	87	87	0.8431	87
Prior DMARD regimens failed	5.5 ± 3.7	5.3 ± 6.0	0.8474	5.4 ± 5.0
Tender joint count	36.2 ± 9.9	36.7 ± 9.2	0.7158	36.5 ± 9.5
Swollen joint count	23.8 ± 9.6	23.9 ± 8.9	0.8997	23.9 ± 9.2
Physician assessment of disease activity	7.6 ± 1.0	7.2 ± 1.3	0.0918	7.4 ± 1.2
Patient assessment of disease activity	7.7 ± 1.1	7.5 ± 1.4	0.4464	7.6 ± 1.3
Patient assessment of pain	7.6 ± 1.2	7.4 ± 1.5	0.5796	7.5 ± 1.3
Health Assessment Questionnaire	1.9 ± 0.6	1.8 ± 0.5	0.1775	1.8 ± 0.6
C-reactive protein	4.0 ± 3.0	4.1 ± 4.0	0.9833	4.0 ± 3.6

Blinding

As noted above, this was a double-blind study. All patients, investigators and nurses attending the patients were blinded to the type of treatment received. One non-blinded nurse or technician handled all set-up and manipulation of the components of the procedure specific to each treatment arm. To maintain the blind, the sponsor designed a circular curtain mounted around a standard IV pole. The curtains were constructed of an opaque material and were designed to permit passage of necessary tubing and allow the entrance of non-blinded staff without exposing the interior components. Prosorba® columns were used in the set-up for the sham patients (as well as the Prosorba® column patients). For the sham patients, the non-blinded staff member turned a valve that caused the plasma to bypass the column and directly enter a plasma transfer bag (that had the same volume as the Prosorba® column). For the Prosorba® column patients, plasma was first routed through the column and then into a plasma transfer bag. After exiting the blinded area, plasma for both groups entered a non-blinded transfer bag prior to returning to the patient. All steps visible to the patient, investigator and nurses were identical between the two treatment arms. A survey was conducted by the sponsor (after the trial enrollment was stopped but prior to unblinding) to determine whether the investigator and study coordinator could guess the treatment group assignment. These data indicated that neither the investigator nor the study coordinator was able to predict the randomization assignment for the patients in this trial. A similar survey of the patients was not performed.

Treatment administration

Patients were pre-medicated 30 minutes prior to the initiation of apheresis with 650 mg acetaminophen and 25-50 mg of Benadryl® to minimize symptoms of complement activation. All treatments utilized a COBE Spectra™ on-line apheresis unit for the separation of plasma from cellular elements. Immediately before treatment, each column was washed with 4 liters of sterile saline and anti-coagulated with 500 ml of saline containing 5,000 units of heparin. After priming of the apheresis machine and the Prosorba® column by the blinded personnel, the unblinded staff member determined the type of treatment by turning a valve so that the plasma either flowed through or bypassed the Prosorba® column. As

discussed above, all elements of the extracorporeal circuit were therefore identical for the two groups, the only difference being whether or not the plasma flowed through the Prosorba® column.

A plasma volume of 1250 ± 250 ml was to be passed through the Prosorba® column for each session. Flow rates were 10 to 20 ml/min. The mean plasma volume treated for the Prosorba® column patients was 1239.8 + 131.7 ml, while the mean plasma volume treated for the sham patients was 1233.1 + 149.4 ml. Effectiveness determinations were based on intent to treat with the last observation carried forward. At least 6 of the 12 treatments and all required follow-up visits had to be performed for patients to be considered to have completed the treatment in the analysis.

Assessments of disease activity

Assessment of disease activity was performed according to the ACR criteria discussed above. These assessments were completed on weeks 5, 9, 13, 16, 19, 20 and 24 by the patient and by either the investigator or his/her designated surrogate evaluator.

Vital signs and other physical findings were monitored during each treatment and at every follow-up visit. Laboratory parameters [i.e., CBC with differential, blood chemistries (electrolytes, glucose, BUN, creatinine, bilirubin, SGOT (AST), alkaline phosphatase, lactate dehydrogenase (LDH)) and total protein] were assessed at baseline and at weeks 5, 9, 13, 16 and 24. Coagulation profile (PT, PTT, fibrinogen) were assessed at baseline and at weeks 5, 13 and 24.

Effectiveness Results

The primary effectiveness analysis includes 99 patients who entered the double-blind, sham-controlled phase of the pivotal trial. Table 3 below summarizes the effectiveness results by treatment arm.

Table 3 - Primary Effectiveness Analysis

	Prosorba® Arm	Sham Arm
Total Randomized	52	47
• Withdrawn	16	15
• Completed All Treatments & Follow-up	36	32
Number ACR Responders	15	5
ACR Response Rate (Of total, n=99)	28.9%	10.6%

Figure 1 (below) graphically illustrates the percentage of ACR responders (i.e., demonstrating a 20% improvement in ACR score) over time for each group. As shown in this Figure, maximal improvement was not obtained until approximately 16 weeks after treatments began.

Figure 1 - Percent of ACR responders in Prosorba® column and sham arms over time.

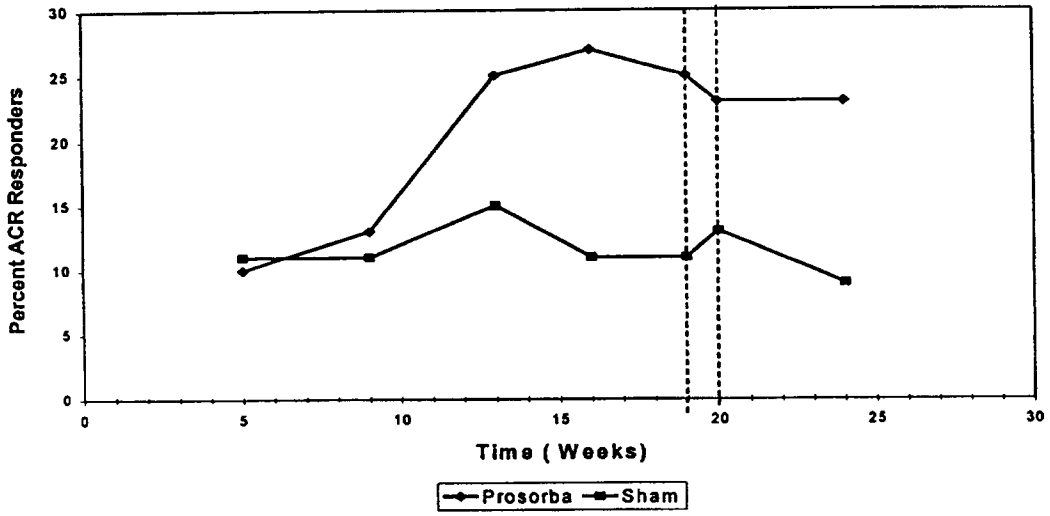

Table 4 below, shows the mean ACR component scores over time for both Prosorba® and sham patients for weeks 19, 20 and 24.

Response Duration

Response duration of the Prosorba® column treated patients was calculated as a survival analysis, using the SAS LIFETEST procedure to determine mean and median survival (of response). The mean and median duration of improvement were 37.0 ± 5.3 and 32 weeks, respectively.

Protocol Deviations

The protocol deviations were collected on the total 109 patients and were classified as follows:

- Patients who entered the study who did not meet inclusion/exclusion criteria
- Patients who developed withdrawal criteria during the study
- Patients who received an incomplete dose
- Patients who received an excluded concomitant treatment

With regard to the inclusion/exclusion criteria, there were 5 cases of inadequate washout of DMARDs. Six patients were on "non-stable" doses of NSAID prior to study entry. Two patients received prior anti-CD4 therapy. Three patients had a history of malignancy within 5 years. One patient had 15 instead of 20 painful and 8 instead of 10 swollen joints. One patient exhibited morning stiffness of less than 60 minutes duration.

Table 4. - Mean ACR Component Scores Over Time for Both Prosorba® and Sham patients at Weeks 19, 20 and 24 (n=99)

ALL PROSORBA PATIENTS (N=52)							
	Baseline	Week 19		Week 20		Week 24	
Parameter	Value	Average	Decrease	Average	Decrease	Average	Decrease
Tender Joints	36.7	23.5	35.3%	23.3	36.8%	27.8	25.2%
Swollen Joints	23.9	18.3	24.9%	17.6	28.6%	20.1	15.4%
Patient Pain	7.4	5.4	24.4%	5.7	22.6%	6.5	11.1%
Patient Global	7.5	5.4	24.6%	5.5	23.4%	6	17.7%
MD Global	7.2	5.2	25.0%	5.9	16.5%	5.7	19.7%
HAQ	1.8	1.6	1.6%	1.6	3.5%	1.7	-0.6%
CRP	4.0	3.7	16.2%	3.6	18.9%	4	6.4%
ALL SHAM PATIENTS (N=47)							
	Baseline	Week 19		Week 20		Week 24	
Parameter	Value	Average	Decrease	Average	Decrease	Average	Decrease
Tender Joints	36.2	34	10.3%	30.8	17.7%	31.6	15.3%
Swollen Joints	23.8	21.5	10.3%	19.6	18.9%	19.6	20.3%
Patient Pain	7.6	6.7	7.0%	6.7	7.5%	6.3	11.7%
Patient Global	7.7	6.8	7.5%	6.7	10.5%	6.3	13.3%
MD Global	7.6	6.3	15.7%	6.4	13.2%	6.4	13.2%
HAQ	1.9	1.8	4.4%	1.7	4.2%	1.7	7.3%
CRP	4.0	4.1	-9.8%	3.6	0.1%	3.5	2.1%
PROSORBA RESPONDERS (N=15)							
	Baseline	Week 19		Week 20		Week 24	
Parameter	Value	Average	Decrease	Average	Decrease	Average	Decrease
Tender Joints	35.9	11.8	67.4%	12.1	65.5%	14.3	60.5%
Swollen Joints	24.0	12.2	53.1%	10.5	60.7%	13.9	42.9%
Patient Pain	7.7	3	60.3%	3.6	51.8%	4.8	37.5%
Patient Global	7.7	3.1	58.4%	3.4	52.4%	3.8	49.3%
MD Global	7.0	3.1	54.8%	4.2	38.7%	3.5	50.6%
HAQ	1.8	1.3	27.6%	1.3	27.4%	1.4	21.8%
CRP	3.5	2.6	19.8%	2.4	22.6%	2.8	0.1%

There were 76 occurrences of excluded concomitant medication. Steroids were the most common therapy initiated with 41 occurrences in 21 patients. Pulse steroid treatment was used to maintain patients in the trial. However, only two of the patients who received steroid pulse therapy were classified as responders, and they only received the steroids after the primary effectiveness endpoint at weeks 19 and 20.

There were two patients who were treated with DMARDs (4 occurrences) during the study (1 Prosorba® and 1 sham patient). One of these patients was listed as a drop-out (the sham patient), and the other was classified as a non-responder (the Prosorba® patient). One patient received cyclosporin and was classed as a non-responder (sham). In addition, 10 patients began therapy with a new NSAID during the treatment and follow-up period, and 13 patients reported 20 occurrences of non-stable NSAID use during the study. However, these changes were minimal and did not affect the primary endpoint.

Steroidal joint injections were not recorded as protocol deviations since they were permitted under the protocol. However, whenever a joint was injected, it was classified as tender and swollen for the remainder of the trial.

Study Drop-outs

Of the 109 patients randomized, there were 31 drop-outs, 16 for the Prosorba® column and 15 for the sham arm. One patient in the Prosorba® column arm actually discontinued at week 20 but since the time for the primary endpoint was reached, this patient was not counted as a withdrawal. The disposition of patients are given in detail in Table 5 below.

Table 5: Patient Disposition in randomized trial.

Patient Disposition N = 99	
Prosorba N = 52	Sham N = 47
Completers N = 36 Withdrawn N = 16	Completers N = 32 Withdrawn N = 15
• Lack of effectiveness (LOE) = 5 • Adverse Event (AE) = 7 • Venous Access problems = 2 • Lost to follow-up (LTFU) = 1 • Protocol Violation = 1	• LOE = 4 • AE = 5 • Venous Access problems = 3 • LTFU = 2 • Protocol Violation = 1

Safety Analysis

The most common adverse events (i.e., those that occurred in greater than 10% of the patients) are provided in 6 below.

Table 6 - Most Common Adverse Events by Treatment Arm during RA Pivotal Study (N=109)

	Number/Percent of Patients w/ AE[1]		Number/Percent of Treatments w/ AE[2]	
Adverse Event (AE)	Prosorba®	Sham	Prosorba®	Sham
Joint Pain	46 (82%)	37 (70%)	249 (44%)	217 (45%)
Fatigue	31 (55%)	23 (43%)	103 (18%)	132 (27%)
Joint Swelling	29 (52%)	24 (45%)	137 (24%)	150 (31%)
Hypotension	21 (38%)	15 (28%)	40 (7%)	27 (6%)
Nausea	20 (36%)	15 (28%)	30 (5%)	28 (6%)
Pain, Abdominal	17 (30%)	12 (23%)	18 (3%)	14 (3%)
Flushing	16 (29%)	8 (15%)	20 (3%)	10 (2%)
Paresthesia	14 (25%)	12 (23%)	47 (8%)	24 (5%)
Headache	14 (25%)	10(19%)	36 (6%)	26 (5%)
Hematoma	14 (25%)	10 (19%)	19 (3%)	15 (3%)
Dizziness	13 (23%)	18 (34%)	22 (4%)	35 (7%)
Sore Throat	12 (21%)	7 (13%)	23 (4%)	12 (2%)
Rash	12 (21%)	4 (8%)	23 (4%)	12 (2%)
Diarrhea	12 (21%)	8 (15%)	14 (2%)	26 (5%)
Edema	11 (20%)	13 (25%)	29 (5%)	24 (5%)
Hypertension	10 (18%)	6 (11%)	26 (5%)	4 (1%)
Pain, Generalized	10 (18%)	9 (17%)	15 (3%)	14 (3%)
Chills	10 (18%)	7 (13%)	16 (3%)	15 (3%)
Dry Mouth	10 (18%)	0 (0%)	6 (1%)	0 (0%)
Nervousness	9 (16%)	11 (21%)	16 (3%)	22 (5%)
Anemia	8 (14%)	8 (15%)	29 (5%)	18 (4%)
Pain, Chest	8 (14%)	2 (4%)	10 (2%)	4 (1%)
Respiratory Difficulties	7 (13%)	5(9%)	8 (1%)	5 (1%)
Fever	7 (13%)	12 (23%)	4 (1%)	9 (2%)
Muscle Tightness	6 (11%)	6 (11%)	14 (2%)	16 (3%)
Itching/hives	6 (11%)	3 (6%)	6 (1%)	9 (2%)
Infection	6 (11%)	5 (9%)	4 (1%)	7 (1%)
Twitching	2 (4%)	6 (11%)	6 (1%)	10 (2%)
Number of AE/pt	27.4	26.1		
Number of AE/pt-treatment			2.8	2.8

[1]Number of AE's includes those observed during treatment and assessment/follow-up visits.
[2]Number of AE's includes only those observed during the 12 treatments.

Adverse events that were observed in less than 10% of the patients included: tinnitus, insomnia, spasm, hypovolemia, bronchitis, sinusitis, vasovagal reactions/syncope, tachycardia, coagulation abnormalities/thrombosis, constipation, tremors, vomiting, gastritis, flu-like symptoms, cough, sepsis, injection site reaction, weight loss, muscle aches, palpitations, hair loss, joint stiffness, dental diseases, vasoconstriction, flatulence, arrhythmia, ear pain, neck pain, urticaria, bone pain, petechiae, red cell split, hemolysis, allergic reaction, photophobia, ACDA reaction, Baker's cyst, depression, dyspepsia, hyperthyroidism/elevated T4, hematuria, osteopenia, thrush, myasthenia, bloody nose, bradycardia, vitreous disease, hyperglycemia, hypokalemia, laryngitis, lymphadenopathy, pericarditis, rhinitis,

glossitis, sweating, enlarged abdomen, back pain, ileitis, dysphagia, taste perversion, hair breakage, injection site pain, injection site hemorrhage, urinary tract infection, gastroenteritis, throat tightness, blurred vision, vasculitis, impaired concentration, agitation, amnesia, decreased renal function, dry eyes, incontinent bladder/bowel, labyrinthitis, malaise, mouth sores, polyuria, skin ulcer, amenorrhea, anorexia, melena, somnolence, skin discoloration, conjunctivitis, hyperkinesia, scleritis, thrombocytopenia, and bursitis.

There were a total of 2,920 adverse events in study; 1,561 occurred in the Prosorba® treated patients and 1,359 occurred in the sham treated patients. Of the total adverse events, there were 44 serious complications (21 in 12 Prosorba® treated patients and 23 in 8 sham- treated patients) and 17 adverse events leading to hospitalizations (11 in the Prosorba® and 6 in the sham patients). Two deaths were observed during the study, both in the sham group. One death occurred nine months after treatment as a probable result of sequelae stemming from a central catheter infection. The second patient died seven months after treatment due to complications following surgery for cholecystitis.

With regard to laboratory values, there were significant changes over time in hemoglobin, hematocrit, and MCV. The average hematocrit fell from approximately 43 at baseline to 37 at week 24 and the average decrease in hemoglobin was 11.5% for the Prosorba® column group and 12.7% for the sham group. One patient in the study (Prosorba® group) received a transfusion due to anemia related to the treatment. The changes over time for hemoglobin, hematocrit, MCV and RBC are given in Table 7 below. These changes were attributed to the apheresis procedure, the effects of blood drawing and the anemia of chronic illness that is apparent for many RA patients. A warning has been included in the labeling to monitor patients for anemia during treatment and follow-up.

Five of the nine patients who received central venous access lines experienced complications related to their use. Among these five patients were three sham-treated patients who developed infections: (1) one sham patient developed a localized catheter infection and thrombosis; (2) the second sham patient experienced infection and thrombosis at the catheter site with subsequent *Staphylococcal* sepsis; (3) the third sham patient developed secondary septic pulmonary emboli due to a central line infection. In addition, two Prosorba® patients experienced complications secondary to central lines: (1) one patient developed an irreversible thrombosis; (2) the second patient experienced an episode of catheter site hemorrhage, followed by irreversible thrombosis at a later treatment. A warning has been included in the labeling that central venous access lines should be used with caution in RA patients.

Two of the most commonly reported adverse events during the pivotal trial were joint pain and joint swelling. A post-treatment "flare" was characterized as an acute exacerbation of joint pain and swelling, with onset typically between 2 and 24 hours after treatment, usually lasting from 12 to 72 hours. It was determined that 19/52 (37%) of Prosorba® treated patients and 13/47 (28%) of sham-treated patients reported at least one episode of a post-treatment flare.

A statistically significant change in platelet count over time was observed. This change (an apparent 8% increase) was the same in both treatment groups. A minimal baseline neutrophilia was also observed, similar in both treatment arms, thought to be secondary to underlying disease and steroid usage. This neutrophilia was stable and without change during the course of the trial. There were no changes in lymphocytes or bands during the course of the trial.

There were no significant changes over time in mean or median values of any of the tests used to assess hepatic or renal function. Serum electrolytes were all within normal limits, with no changes over time nor differences between treatment groups. INR and PTT mean and median values remained normal throughout the trial. The mean levels of fibrinogen were uniformly elevated but this was attributed to the

patients' underlying disease. There was no significant change over time in fibrinogen levels and no differences were observed between the two groups.

Table 7 - Changes over time in H/H, MCV, RBC Count for sham and Prosorba® patients (N=99)

	Hemoglobin		*Hematocrit*		*MCV*		*RBC*	
	Sham	*Prosorba*	*Sham*	*Prosorba*	*Sham*	*Prosorba*	*Sham*	*Prosorba*
Visit	N=47	N=52	N=47	N=52	N=47	N=52	N=47	N=52
Baseline	13.6 ± 1.6	13.4 ± 1.8	42.8 ± 5.3	42.2 ± 5.5	95.5 ± 10.8	92.3 ± 8.4	4.5 ± 0.6	4.6 ± 0.7
Week 5	12.4 ± 1.7	11.4 ± 1.5	39.0 ± 5.1	35.7 ± 4.6	91.8 ± 9.0	88.0 ± 8.0	4.3 ± 0.6	4.1 ± 0.4
Week 9	11.7± 1.7	11.2 ± 1.5	36.2 ± 4.9	34.9 ± 4.5	89.5 ± 8.4	86.7 ± 7.9	4.1 ± 0.5	4.0 ± 0.4
Week 13	11.8 ± 1.9	11.5 ± 1.8	36.6 ± 5.2	36.1 ± 5.3	86.9 ± 7.2	84.1 ± 8.8	4.2 ± 0.5	4.3 ± 0.4
Week 16	11.9 ± 2.1	11.7 ± 1.7	37.1 ± 5.3	36.6 ± 4.9	85.0 ± 8.1	83.0 ± 9.0	4.4 ± 0.5	4.4 ± 0.4
Week 24	12.2 ± 1.9	11.9 ± 1.8	38.0 ± 5.3	37.3 ± 5.1	82.7 ± 8.8	82.7 ± 9.4	4.5 ± 0.8	4.5 ± 0.5

D. RA Open-Label Study

The pivotal study was designed with an additional, open-label arm called the "continuation phase." This arm was designed to provide patients who completed the core phase of the trial (12 weeks treatment plus 12 weeks follow-up) the opportunity to obtain Prosorba® treatment, regardless of their original assignment. Patients and caregivers remained blinded to the treatment that was given during the core phase.

The core phase of the study was originally designed to enroll 268 patients at 12 sites. However, after a second interim analysis (performed on January 9, 1998) an external data safety monitoring board recommended that the trial be stopped early because a statistical difference between the two treatment arms was observed. At the time that the trial was stopped, there were 10 patients who were actively receiving treatment. For ethical considerations, these patients were "rolled over" into the open-label continuation phase. The continuation phase thus enrolled a total of 50 patients: 40 who had completed the core phase and 10 who were "roll-over" patients.

The re-enrollment rate for patients who completed the core phase was 75%. The primary effectiveness endpoint was an assessment at weeks 20 or 24. To compute the response, a comparison was made between (1) the average of three baseline assessments performed prior to the core phase treatments and (2) either the week 20 or week 24 continuation phase assessment. If both of the latter two assessments were available, the better of the two was used. Similar to the Core Phase, laboratory safety evaluations included hematologic, clinical chemistry and coagulation studies performed at baseline, week 7 or 9 and week 13. Of the 50 patients enrolled, twelve patients dropped out during the continuation phase; 5 due to lack of effectiveness, 5 for adverse events, 1 for blood access difficulties and 1 because the investigator discontinued the study.

The effectiveness results for the patients enrolled in the continuation phase are shown in Table 8. An overall 34% response rate was observed (based on intent-to-treat).

Table 8 - Continuation Phase Effectiveness Analysis (N=47)

Continuation Analyses: All Continuation Patients (N=50) based on treatment randomization	Prior Core Phase: Prosorba® Treatment	Prior Core Phase: Sham Treatment	Patients "Rolled over" to Continuation Phase	Continuation Phase Total
Total Continuation Patients	23	18	9	50
Continuation Patients Excluded*	1	0	0	1
Continuation Efficacy Analysis "Intent to Treat"	*22*	*18*	*9*	*49*
Continuation Patients Dropped	6	2	4	12
Continuation Patients Completed	16	16	5	37
Number of ACR Responders	7	7	3	17
Percent ACR Responders	31.8%	40.0%	33.3%	34.7%

* One patient (1021) used a Paulus core phase baseline instead of the ACR criteria baseline, so has been excluded.

Only limited data are available on patients who received more than one treatment course. Seven patients who were non-responders to the Prosorba® column in the first phase of the study received a second treatment during the continuation phase. None (0%) of these patients responded to the second treatment. Ten patients who were responders to the Prosorba® column in the first phase were retreated in the continuation phase. Seven of these patients (70%) responded a second time. Due to the preliminary nature of these data, a post-market study is planned to evaluate the safety and effectiveness of retreatment with the Prosorba® column for RA patients.

The adverse events for the continuation phase that occurred in 10% or more of the patients are shown in Table 9 below. The observed adverse events were similar to those observed in the core study. The adverse events that were observed in less than 10% of the patients included: muscle aches, flatulence, dyspepsia, cough, insomnia, nervousness, hematoma, tachycardia, fever, gastritis, coagulation abnormalities/thrombosis, tinnitus, spasm, joint stiffness, bone pain, rhinitis, neck pain, sweating, infection, twitching, urinary tract infection, dental diseases, bursitis, vasculitis, impaired concentration, skin discoloration, muscle tightness, vasovagal reactions, vomiting, allergic reaction, bronchitis, dry eyes, dry mouth, flu-like symptoms, glossitis, taste perversion, tremors, itching/hives, throat tightness, urticaria, blurred vision, cyanosis, depression, hair loss, malaise, mouth sores, ear pain, somnolence.

Table 9- Adverse Events Observed in Open-Label Continuation Phase (N=50)

Adverse Event (AE)	Number/ Percent of Patients w/ AE[1]	Number of Treatments w/ AE[2]
Joint Pain	39 (78%)	161 (35%)
Joint Swelling	29 (58%)	135 (29%)
Fatigue	16 (32%)	104 (22%)
Headache	14 (28%)	25 (5%)
Dizziness	13 (26%)	12 (3%)
Other	12 (24%)	30 (6%)
Nausea	10 (20%)	25 (5%)
Pain, Abdominal	9 (18%)	27 (6%)
Anemia	7 (14%)	21 (5%)
Diarrhea	7 (14%)	7 (2%)
Chills	7 (14%)	5 (1%)
Edema	6 (12%)	23 (5%)
Hypertension	6 (12%)	26 (6%)
Paresthesia	6 (12%)	23 (5%)
Flushing	6 (12%)	12 (3%)
Pain, Generalized	6 (12%)	7 (2%)
Pain, Chest	6 (12%)	6 (1%)
Sinusitis	5 (10%)	11 (2%)
Respiratory Difficulties	5 (10%)	11 (2%)
Dyspepsia	5 (10%)	9 (2%)
Hypotension	5 (10%)	10 (2%)
Sore Throat	5 (10%)	10 (2%)
Rash	5 (10%)	8 (2%)
Number of AE/pt	23.5	[redacted]
Number of AE/pt-treatment	[redacted]	2.0

[1]Number of AE's includes those observed during treatment and assessment/follow-up visits.
[2]Number of AE's includes only those observed during the 12 treatments.

X. PANEL RECOMMENDATIONS

At an advisory panel meeting held on October 29, 1998, the Gastroenterology and Urology Device Panel recommended that Cypress Bioscience's PMA supplemental application be approved, subject to submission of and approval by the Center for Devices and Radiological Health (CDRH) the following:

A. Labeling

1. In addition to the already approved indication for ITP, the device is to be indicated for use in the therapeutic reduction of the signs and symptoms of rheumatoid arthritis (RA) in adults with long-standing, moderate to severe

rheumatoid arthritis who have failed or are intolerant to disease modifying anti-rheumatic drugs (DMARDs).

2. The labeling should include a strong warning to both the patient and the healthcare provider about the risks of using central venous access lines.

B. A post-approval study is required to collect data on the following:

1. The long-term safety and effectiveness of re-treatment with the Prosorba® column for RA patients; and

2. The long-term safety and effectiveness of treatment with the Prosorba® column in combination with DMARDs.

XI. CDRH DECISION

CDRH concurred with the Panel's recommendation regarding labeling and the need for a post-approval study. CDRH believes a post-approval study is necessary in order to gather information on the long-term safety and effectiveness of the device in the target population. When the post-approval study is completed, the results will be reflected in the device labeling. Cypress Bioscience, Inc. provided the additional information to their PMA application and CDRH issued an approval order on March 15, 1999 for the stated indication.

FDA inspection determined the manufacturing facilities to be in compliance with GMPs.

XII. APPROVAL SPECIFICATIONS

Directions for Use: See Professional labeling .

Post-approval study: The sponsor has agreed to conduct a post-approval study to collect data on the long-term safety and effectiveness of the Prosorba® column in the target population.

The sale, distribution and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug and Cosmetic Act (the Act) under authority of section 515(d)(1)(B)(ii) of the Act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution and use must not violate sections 502(q) and (r) of the Act.

Warnings, Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Effects in the attached labeling.

XIII. REFERENCES

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