May 25, 2012

Office of Medical Device Evaluation
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

[Classification]	Instrument & Apparatus 7 Organ function replacement device
[Generic name]	Leukocytapheresis device
[Brand name]	Adacolumn
[Applicant]	JIMRO Co., Ltd.
[Date of application]	September 21, 2011 (application for partial change)

[Results of deliberation]
In the meeting held on May 25, 2012, the Committee on Medical Devices and *In-vitro* Diagnostics made the following decision, and concluded that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

Adacolumn may be approved with a re-examination period of 7 years. The product is not classified as a biological product or as a specified biological product.

Review Report

May 8, 2012

Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following medical device submitted for registration are as follows.

[Classification]	Instrument & Apparatus 7	Organ function replacement device
[Generic name]	Leukocytapheresis device	
[Brand name]	Adacolumn	
[Applicant]	JIMRO Co., Ltd.	
[Date of application]	September 21, 2011	
[Items warranting special mention]	Orphan medical device	
[Reviewing office]	Office of Medical Devices II	

Review Results

May 8, 2012

[Classification]	Instrument & Apparatus 7	Organ function replacement device
[Generic name]	Leukocytapheresis device	
[Brand name]	Adacolumn	
[Applicant]	JIMRO Co., Ltd.	
[Date of application]	September 21, 2011 (application for partial change)	

[Results of review]
Adacolumn is a column for apheresis (an adsorptive-type apheresis device) designed to control inflammatory reactions and to improve pathological conditions by removing granulocytes and other leukocytes from the peripheral blood via adsorption. It was approved in October 1999 for inducing remission of severe active ulcerative colitis; it was approved in September 2008 for inducing remission in patients with moderate to severe active Crohn's disease, who have failed to respond to or are ineligible for nutritional intervention or existing pharmacotherapies, with persisting evident clinical symptoms resulting from lesions in the large intestine. Recently, an application was filed for approval of a partial change, which involves the addition of "treatment of clinical symptoms of pustular psoriasis" to its intended use. Adacolumn was designated as an orphan medical device in July 2009 for this intended use.

A multicenter, open-label, uncontrolled study in 15 patients with moderate to severe pustular psoriasis to evaluate the efficacy and safety of Adacolumn was conducted in Japan (11 sites). In this clinical study, the clinical usefulness of Adacolumn were evaluated 2 weeks after the last day of apheresis treatment, based on efficacy evaluation scores calculated by adding the erythema color improvement scores to the severity scores specified in the Therapeutic Guidelines for Generalized Pustular Psoriasis, as well as overall safety. Patients were classified as responders when treatment reduced their pretreatment score by 40% at the time of efficacy evaluation. All 15 patients had generalized pustular psoriasis. Of these, 1 patient who discontinued the treatment and 2 patients who deviated from the protocol were excluded from analyses. Of the remaining 12 patients, 11 patients were responders (response rate of 91.7%). With regard to safety, adverse events potentially related to apheresis with Adacolumn included headache, dizziness, dizziness on standing up, chilliness, and feeling of weakness (all moderate), as well as slight shadows in the lung, mild worsening of bullous pemphigoid. These adverse events posed no significant clinical issues. Although this clinical study was an uncontrolled study enrolling a small number of subjects, evaluation of the efficacy of Adacolumn was considered feasible because the subjects had failed to respond to virtually all existing pharmacotherapies, the study was designed to include a certain prior treatment period in order to minimize the effects of previous therapies, and evaluation scores indicated improvements in clinical symptoms. Since no effective therapy for moderate to severe pustular psoriasis is currently available, the introduction of Adacolumn to medical practice is considered clinically significant.

Based on its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that Adacolumn may be approved for the following intended use, modified as shown below, and

that this result should be deliberated at the Committee on Medical Devices and *In-vitro* Diagnostics.

[Intended use]
Adacolumn is used to treat clinical symptoms of patients with moderate to severe pustular psoriasis in who failed to respond or are ineligible for existing oral systemic therapies.

Review Report

May 8, 2012

I. Product for Review

[Classification] Instrument & Apparatus 7 Organ function replacement device
[Generic name] Adsorptive-type apheresis device
[Brand name] Adacolumn
[Applicant] JIMRO Co., Ltd.
[Date of application] September 21, 2011
[Proposed intended use] Treatment of clinical symptoms of pustular psoriasis
[Items warranting special mention]
Orphan medical device

II. Product Overview

Adacolumn is a column for apheresis designed to control excessive inflammatory reactions and to improve pathological conditions by removing granulocytes and other leukocytes from the peripheral blood via adsorption (Figure 1). It was approved in October 1999 for inducing remission of severe active ulcerative colitis (approval number, 21100BZZ00687000). In September 2008, a partial change application for addition of a new intended use was approved to include induction of remission in patients with moderate to severe active Crohn's disease, who have failed to respond to or are ineligible for nutritional intervention or existing pharmacotherapies, with persisting evident clinical symptoms resulting from lesions in the large intestine. Recently, an application was filed for approval of a partial change involving the addition of "treatment of clinical symptoms of pustular psoriasis" to its intended use. Adacolumn is filled with 220 g of cellulose acetate processed into beads as the adsorptive carrier. Adacolumn is to be used in apheresis treatment at a flow rate of 30 mL/min for 60 minutes once a week over a period of 5 consecutive weeks (1 course).

In July 2009, Adacolumn was designated as an orphan medical device whose proposed intended use is "treatment of clinical symptoms of patients with pustular psoriasis."

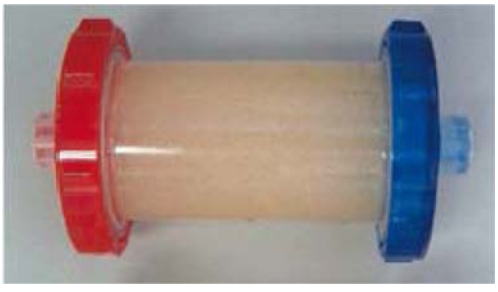

Figure 1. Appearance of Adacolumn

III. Summary of the Submitted Data and Outline of the Review by the Pharmaceuticals and Medical Devices Agency

The data submitted by the applicant in the application and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.
The expert advisors for the Expert Discussion on this product declared that they do not fall under Item 5 of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/20 dated December 25, 2008).

1. Origin or history of discovery and usage conditions in foreign countries, etc.

[Origin or history of discovery]

Pustular psoriasis is an intractable skin disease with inflammatory features including erythema accompanied by general symptoms such as pyrexia and malaise; multiple aseptic pustules; an increase in the number of polymorphonuclear leukocytes in the peripheral blood; and neutrophilic infiltration in the skin. The disease is rare, with approximately 2000 patients in Japan. Generalized pustular psoriasis, which involves the entire body, has been designated as a rare and intractable disease. Available therapies include oral drugs such as etretinate and cyclosporine; topical agents such as steroid and vitamin D_3; and ultraviolet irradiation (phototherapy with PUVA or NB-UVB). Nevertheless, treatment effect is inadequate for some patients, and clinically significant adverse drug reactions such as growth disorders, teratogenicity, and hepatic and renal disorders have been reported with oral drugs. In addition, while the recently introduced biological product (infliximab) is clinically effective, clinically significant adverse drug reactions such as infections and serious infusion reactions have been reported. Therefore, new therapeutic options are expected to be introduced to the clinical practice. Adacolumn has been approved for inducing remission in patients with severe active ulcerative colitis, and for inducing remission in patients with moderate to severe active Crohn's disease, who have failed to respond to or are ineligible for nutritional intervention or existing pharmacotherapies, with persisting evident clinical symptoms resulting from lesions in the large intestine. Its safety within the scope of approved applications has already been demonstrated. Adacolumn's ability to remove granulocytes from the blood has been confirmed, which may also reduce erythema, aseptic pustules, and other inflammatory manifestations. For these reasons, an application has recently been filed to add a new intended use for Adacolumn (namely, alleviating symptoms of pustular psoriasis), claiming that Adacolumn may also be used to treat pustular psoriasis.

[Usage conditions in foreign countries and occurrence of malfunctions]

Since Adacolumn has not been approved as a medical device to treat pustular psoriasis in foreign countries, it has never been sold for the proposed intended use.

Adacolumn is allowed to be CE marked as a medical device for the treatment of inflammatory bowel disease (ulcerative colitis, Crohn's disease), rheumatoid arthritis, Behcet's disease, and systemic lupus erythematosus in 15 European countries, and [redacted] units were distributed from 2002 to the end of December 2011. It was also approved in China in September 2011 as a medical device for the treatment of inflammatory bowel disease, although Adacolumn has yet to be marketed as of April 2012.

Until September 21, 2011, no malfunctions had been reported in Europe that could have triggered recalls. To date, 11 adverse events for which a causal relationship to Adacolumn could not be ruled out have been reported, of which 6 qualified for 15-day or 30-day regulatory reporting. However, all were common symptoms associated with apheresis treatment, and the outcome was recovery in all cases.

In Japan, [redacted] units of Adacolumn have been distributed as of the end of March 2012 for use within the scope of the approved intended use. Up to that date, 162 adverse events have been reported in association with treatment of ulcerative colitis, of which 10 (e.g., shock, abnormal hepatic function) qualified for 15-day regulatory reporting. Likewise, 95 adverse events have been reported in association with treatment of Crohn's disease, but none qualified for regulatory reporting.

2. Physicochemical properties and specifications

This application has been filed for a partial change involving the addition of an intended use. Thus, no new study data has been submitted.

3. Safety

This application has been filed for a partial change involving the addition of an intended use. Thus, no new study data has been submitted.

4. Electrical safety, biological safety, and other safety-related data

This application has been filed for a partial change involving the addition of an intended use. Thus, no new study data has been submitted.

5. Performance

This application has been filed for a partial change involving the addition of an intended use. Thus, no new study data has been submitted.

6. Clinical data

The results of a multicenter, open-label, uncontrolled study in 15 patients conducted in Japan (11 sites) have been submitted as clinical data. This study was conducted to evaluate the efficacy and safety of Adacolumn in patients with pustular psoriasis in accordance with the Therapeutic Guidelines for Generalized Pustular Psoriasis, 2008 Edition; the severity of the disease in all these patients had been "moderate to severe," based on the severity scores specified in the same guidelines. In principle, each patient was treated once a week for 5 consecutive weeks, with each session of apheresis lasting 60 minutes at a rate of 30 mL/min. The primary endpoint was the percentage of patients who were classified as responders (the response rate) on the treatment evaluation day (2 weeks after the last day of apheresis treatment). The efficacy was evaluated based on the efficacy evaluation scores calculated by adding the erythema color improvement scores (Table 3) to the severity scores specified in the Therapeutic Guidelines for Generalized Pustular Psoriasis (Tables 1 and 2). Patients were classified as responders when treatment reduced their pretreatment score by 40% at the time of evaluation.

Table 1. Severity scores (skin symptoms)

Skin symptom	Severe	Moderate	Mild	None
Area affected by erythema	3 points	2 points	1 point	0 points
Area affected by erythema with pustules	3 points	2 points	1 point	0 points
Edematous area	3 points	2 points	1 point	0 points

Table 2. Severity scores (systemic symptom/laboratory data)

Systemic symptom/Laboratory data	2 points	1 point	0 points
Body temperature (°C)	≥38.5	≥37 and <38.5	<37
Leukocyte count (/μL)	≥15,000	≥10,000 and <15,000	<10,000
CRP (mg/dL)	≥7.0	≥0.3 and <7.0	<0.3
Serum albumin (g/dL)	<3.0	≥3.0 and <3.8	≥3.8

Table 3. Erythema color improvement scores

Baseline \ Evaluation day	Severe	Moderate	Mild
Severe	0	−1	−2
Moderate	1	0	−1
Mild	2	1	0

The secondary endpoints were (a) the response rate on the day of secondary evaluation (the day of the third apheresis session); (b) changes from baseline values in the Dermatology Life Quality Index (DLQI); (c) changes in severity scores at each evaluation time point (change from baseline values on the day of secondary evaluation and on the treatment evaluation day); and (d) the pathological condition evaluated on the day of the prognosis study (8 weeks after the treatment evaluation day). The safety of Adacolumn was to be evaluated in a comprehensive manner based on all accompanying symptoms, changes in laboratory data, and malfunctions. The rules applied to concomitant treatment are as follows: patients were excluded on the day of baseline examination/observation if (a) they had received any investigational drug, used another investigational device for apheresis or treatment of pustular psoriasis, or apheresis had been recommended for treatment within the past 168 days (6 months); (b) they had received a biological product within the past 56 days (8 weeks); (c) they had started etretinate, cyclosporine, methotrexate, or a topical agent for treatment of pustular psoriasis (e.g., topical steroid, topical vitamin D_3) or had dosage of these agents altered within the past 14 days; (d) they had received phototherapy (PUVA, UVA, UVB) within the past 14 days; (e) they had commenced an oral steroid or had the dosage altered within the past 7 days; and (f) they had received a nonsteroidal anti-inflammatory drug within the past 7 days (unless prescribed for non-anti-inflammatory purpose or as a topical agent).

The response rate based on the evaluation scores in the Full Analysis Set (FAS; n = 14) (Figure 2) consisting of all patients except 1 patient (who discontinued treatment before efficacy evaluation after experiencing an adverse event when undergoing the first apheresis session) was 85.7% (12 of 14 patients). The response rate was 91.7% (11 of the 12 patients) in the Per Protocol Set (PPS; n = 12) (Figure 2), which consisted of the FAS except for 2 patients who deviated from the protocol.

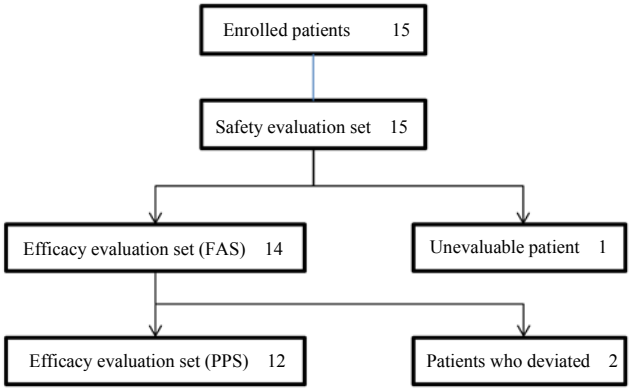

Figure 2. Patient disposition

Of the patients enrolled in the clinical study, 2 patients discontinued treatment. One patient experienced headache and shivering approximately 40 minutes after the start of the initial session of apheresis treatment. Since these adverse events were most likely attributable to the anticoagulant agent (nafamostat mesilate), apheresis was discontinued, and the patient discontinued the treatment without undergoing observation of skin symptoms required for efficacy evaluations. The other discontinued treatment after experiencing an aggravation of symptoms of the primary disease in the period between the fourth apheresis session and the scheduled fifth apheresis session. However, this patient was not excluded from the FAS or PPS, and an efficacy evaluation was performed. Of the patients enrolled in the clinical study, 2 patients deviated from the protocol: 1 patient had used a transdermal steroid patch 4 days after the initial apheresis session based on the patient's own judgment; the other patient increased the dose of oral steroid from 2 mg to 20 mg 1 day after the third apheresis session because of aggravated bullous pemphigoid associated with pustular psoriasis. Since both cases involved violations of drug-related rules concerning steroids, these patients were excluded from the PPS.

The following results for the secondary endpoints were obtained. (a) Seven patients in the FAS and 6 in the PPS showed early improvement, meeting the efficacy evaluation criterion as early as the day of the secondary evaluation (the day of the third apheresis session), meaning half of the patients showed early improvement. (b) Both the FAS and the PPS showed significant improvements in DLQI, particularly in 4 parameters of symptoms, daily activities, leisure, and work/school (Table 4). (c) The area affected by erythema, the area affected by erythema with pustules, and the edematous area, which were used to determine the severity score, all diminished over time, with significant improvements seen after the clinical study (Table 5). (d) Of the 12 patients who were classified as responders and included in the prognosis study, 11 patients were evaluated for pathological conditions on the day of the prognosis study, and the other 1 patient withdrew from the prognosis study 1 week after completion of treatment at the patient's request. Of the 11 patients, 1 patient experienced a symptomatic relapse, and 10 patients kept the levels of remission similar to those on the treatment evaluation day. The 1 patient with symptomatic relapse exhibited aggravation of the erythematous area (from 50% to 80%) approximately 4 weeks after the start of the prognosis study. However, no change was observed in other skin symptoms, such as pustules and edema, or in laboratory findings.

Table 4. Changes in DLQI and its parameters before and after treatment

		FAS (n = 14)			PPS (n = 12)		
	(Full points)	Before treatment	After treatment	*P* value	Before treatment	After treatment	*P* value
DLQI	(30)	16.6 ± 7.9	9.7 ± 7.8	0.0063*	17.6 ± 7.9	10.8 ± 8.0	0.0149*
Symptoms	(6)	4.0 ± 1.3	2.5 ± 1.6	0.0117*	4.2 ± 1.3	2.6 ± 1.7	0.0199*
Daily activities	(6)	3.7 ± 2.0	2.1 ± 1.9	0.0135*	4.0 ± 2.0	2.4 ± 1.9	0.0299*
Leisure	(6)	3.7 ± 2.2	1.9 ± 2.1	0.0075*	4.0 ± 2.2	2.2 ± 2.2	0.0114*
Work/school	(3)	1.9 ± 1.1	1.0 ± 1.2	0.0185*	1.9 ± 1.2	1.2 ± 1.2	0.0473*
Personal relationships	(6)	1.6 ± 2.2	0.9 ± 1.4	0.0845	1.8 ± 2.3	1.0 ± 1.5	0.0845
Treatment	(3)	1.6 ± 0.9	1.3 ± 1.1	0.1898	1.7 ± 1.0	1.4 ± 1.2	0.3657

Mean ± standard error; Wilcoxon signed-rank test; $P = 0.05$

Table 5. Changes in the parameters of severity scores before, during, and after treatment

	FAS (n = 14)				PPS (n = 12)			
	Before treatment	During treatment	After treatment	*P* value	Before treatment	During treatment	After treatment	*P* value
Area affected by erythema (%)	76.8 ± 13.7	63.1 ± 22.8	47.9 ± 30.7	0.0042*	77.1 ± 14.8	62.4 ± 24.5	48.8 ± 30.3	0.0066*
Area affected by erythema with pustules (%)	24.7 ± 12.8	11.7 ± 14.9	5.2 ± 8.1	0.0031*	24.3 ± 13.8	11.5 ± 15.3	4.0 ± 6.1	0.0051*
Edematous area (%)	26.3 ± 19.1	6.5 ± 7.5	5.3 ± 10.8	0.0014*	26.1 ± 20.7	6.3 ± 8.0	5.4 ± 11.6	0.0033*

Mean ± standard error; Wilcoxon signed-rank test; adjusted $P = 0.025$

The mean number of leukocytes adsorbed by Adacolumn per column among the 14 patients in the FAS, a value calculated by comparing the numbers of leukocytes in the blood before and after passage through the column at the time of the initial perfusion, was $(4.25 \pm 0.57) \times 10^9$ granulocytes; $(0.14 \pm 0.02) \times 10^9$ monocytes; and $(0.15 \pm 0.04) \times 10^9$ lymphocytes. Most of the absorbed leucocytes were granulocytes. The mean rate of adsorption from the peripheral blood among the 14 patients in the FAS was 38.6% ± 3.0% for granulocytes; 26.8% ± 3.4% for monocytes; and 6.0% ± 1.5% for lymphocytes.

With regard to safety, 16 adverse events in 3 patients were reported (Table 6). Since 14 were experienced by a single patient, consisting of symptoms such as headache and dizziness that are commonly associated with Adacolumn, the cases was determined to be "probably related" to the treatment with Adacolumn. All symptoms spontaneously disappeared within a few days. Lung shadows were observed in 1 patient who complained of coughing on the day of the fifth apheresis session. Since chest X-ray, computed tomography (CT), sputum examination, and other observations failed to lead to a definitive diagnosis, the case was reported as one with "shadows in the lungs." Although it was difficult to identify the cause, this adverse event was deemed to be potentially related to disease treatment using Adacolumn based on the following observations: pustular psoriasis is sometimes associated with lung disease[1]; a biological product (infliximab), which may re-activate pulmonary tuberculosis, had been administered to the patient before the present clinical study; and concurrent methotrexate therapy could cause pulmonary complications on rare occasions. Therefore, the case was determined to be "probably related" to the treatment with Adacolumn. The causal relationship in the remaining case was judged to be "unknown," given that a causal relationship between treatment with Adacolumn and the pemphigoid aggravation associated with pustular psoriasis could not be ruled out.

Table 6. Incidence of adverse events

SOC*	Event	Number
Nervous system disorders	Headache	5
	Dizziness	5
	Dizziness on standing up	2
Skin and subcutaneous tissue disorders	Worsening of bullous pemphigoid	1
General disorders and administration site conditions	Chilliness	1
	Feeling of weakness	1
Investigation	Shadows in the lung	1
Total		16

*MedDRA/J 14.0

PMDA asked the applicant to explain the applicant's views on the following points:

(1) The mechanism of action by which Adacolumn induces remission of symptoms in patients with pustular psoriasis should be discussed.

(2) Taking the pathology and other characteristics of pustular psoriasis into consideration, how the efficacy of Adacolumn can be evaluated in the current protocol should be explained, although the clinical study was an uncontrolled study.

(3) According to the exclusion criteria, patients for whom the dose of the therapeutic drug had been increased because of aggravation of the primary disease were excluded from analyses, as this was a deviation from one of the drug-related rules. Thus, patients with disease exacerbation were inevitably excluded from analyses across the board. Rationale of the drug-related rules as exclusion criteria should be explained.

(4) Efficacy evaluations determined only whether or not patients responded to the apheresis with Adacolumn, which may have allowed non-responders to include both patients with no change in symptoms and those with disease aggravation. Judgments regarding the acceptability of the proposed intended use differ depending on whether patients have "no change in symptoms" or "aggravation." The patients with disease exacerbation among those classified as non-responders must be evaluated and discussed in detail.

(5) While the applicant claimed that the intended use of Adacolumn was "to treat clinical symptoms of pustular psoriasis," most of the patients enrolled in the clinical study had not responded to existing therapies. Given this situation, the clinical positioning of Adacolumn should be explained based on the comparison with existing therapies.

(6) The rationale for having performed the prognosis study 8 weeks after the treatment evaluation day and how long Adacolumn's efficacy lasts should be explained.

(7) The efficacy and safety of the repeated treatment with Adacolumn in patients who had initially responded to the treatment with Adacolumnwith but relapsed later should be discussed.

(8) Data from the clinical study did not show the efficacy or safety of Adacolumn in patients with localized pustular psoriasis such as palmoplantar pustulosis. Whether or not the use of Adacolumn in patients with localized pustular psoriasis is justified as an intended use should be explained.

The applicant responded as follows:

(1) The mechanism of action by which Adacolumn inhibits inflammatory reactions is considered to be as follows: leucocyte activation is inhibited and inflammatory reactions are generally subdued because (a) leucocytes that are adsorbed by the column release inflammatory and other factors inside the column and incite reactions similar to those that occur at inflammation sites; (b) even leucocytes not absorbed by the column undergo functional changes after passage through the column, including reduced expression of adhesion factors and reduced ability to produce inflammatory cytokines; (c) adsorption and removal of granulocytes by the column leads to mobilization of immature granulocytes from the bone marrow to the periphery, which are less likely to cause inflammatory reactions.

(2) The applicant determined that it would be difficult to perform a controlled study because of the paucity of patients with pustular psoriasis. For this reason, the applicant conducted a single-arm study with no control group. The applicant deemed that Adacolumn's efficacy could be evaluated in a single-arm study for the following reasons: (a) spontaneous remission would be unlikely since the enrolled patients in the clinical study were those with moderate to severe pustular psoriasis; (b) differences between individuals would be eliminated by comparing the results in the same patient before and after intervention using Adacolumn; and (c) the protocol was designed so that the influence of existing therapies on efficacy evaluations would be eliminated as much as possible. As a result of these study rules specified in the protocol, the patients enrolled in the clinical study were those whose symptoms had not improved despite treatment for a certain period before participation in the clinical study. Thus, scientific efficacy evaluations should be feasible with self-controlled comparisons and measures to minimize the influence of existing therapies.

(3) According to the protocol, treatment is discontinued in patients with exacerbation of the primary disease for which continuation of treatment is difficult. However, patients who have undergone at least 1 session of apheresis using Adacolumn and from whom data for efficacy evaluations have been obtained were included in the FAS, regardless of whether they discontinued treatment or deviated from the protocol. The FAS is defined as the main group for efficacy analysis in this clinical study. In fact, the 1 patient in whom treatment was discontinued because of aggravation of the primary disease was included in both the FAS and the PPS. The 2 patients who deviated from the protocol were excluded from the PPS because of protocol deviation, but both were included in the FAS. Therefore, the clinical study was designed so that patients with aggravation of the primary disease whose protocol deviation was unrelated to the aggravation would be appropriately included in analyses.

The FAS was the main analysis group that included patients with aggravation of the primary disease, while the PPS served as the secondary analysis group to minimize the influence of existing therapeutic drugs on efficacy evaluations. Therefore, the drug-related rules in the exclusion criteria of the clinical study were considered to be appropriate.

(4) Of the 2 patients in the FAS who were classified as non-responders, 1 (who deviated from the protocol with the use of steroid patches for cracks on the fingertips) had been enrolled in the clinical study after withdrawing from an oral steroid. On the day of evaluation 2 weeks after the fifth apheresis session with Adacolumn, this patient's laboratory data were found to have worsened. Consequently, the patient's severity score increased, and the patient was classified as a non-responder. Despite worsening of laboratory data, the increase in body temperature was mild, and the change in the C-reactive protein (CRP) level was within the normal range. Regarding the separate skin symptoms that were converted into scores, no aggravation of erythema was observed, and edema was found to

have improved. Although this patient was classified as a non-responder, the patient's symptoms did not change significantly.

The other patient (for whom treatment was discontinued because of aggravation of the primary disease) developed a fever at the time of the fourth apheresis session with Adacolumn, and treatment was eventually discontinued because symptoms had worsened. Since both laboratory data and skin symptoms had worsened at the time of discontinuation, this patient was classified as a non-responder who showed the aggravation of primary disease. Nevertheless, signs of improvement were observed on the day of the secondary evaluation, and disease severity returned to pre-treatment level after discontinuation. From this observation, the applicant considered that despite the risk of disease exacerbation with treatment continuation using Adacolumn, the adverse effect was reversible on discontinuation.

Since the applicant individually evaluated each subject who was classified as a non-responder and found all the assessment acceptable, the efficacy evaluation of Adacolumn is considered appropriate. However, since use of Adacolumn may aggravate symptoms or exhibit no apparent therapeutic effect, the applicant must take measures to reduce risks as much as possible by advising users to discontinue Adacolumn and take appropriate measures if any abnormalities are noted such as aggravation of symptoms or by cautioning them against prolonged use of Adacolumn without careful consideration.

(5) Due to the clinically significant adverse drug reactions such as hepatic and renal disorders, growth disorders, teratogenicity, and the occurrence of malignant tumors associated with drugs that are indicated for pustular psoriasis, those prescribing or administering such drugs are reminded to carefully weigh the benefits and risks of their use and to obtain informed consent from patients. In addition, a safe and effective treatment method that does not excessively burden patients is needed because of the increased incidence of adverse drug reactions caused by drug accumulation with long-term use and the heavy burden on patients, including the need for periodic X-rays and blood tests, with currently available treatments. Infliximab does not have a high safety profile, as it is associated with adverse drug reactions such as anaphylactoid reactions, lupus-like syndrome, demyelinating disease, and non-melanoma skin tumor, along with paradoxical adverse drug reactions such as induction and aggravation of pustules.[2]

On the other hand, Adacolumn has been in use for more than 10 years in Japan for inducing remission of severe active ulcerative colitis and active Crohn's disease. Its safety is highly regarded. The clinical study clearly showed that Adacolumn was therapeutically useful for patients with moderate to severe pustular psoriasis who had failed to respond to existing therapies. No serious or clinically significant adverse events have been reported, and the response rate calculated by the evaluation method based on the severity scores specified in the Therapeutic Guidelines for Generalized Pustular Psoriasis was 85.7% (FAS, 12 of 14 patients). Although rigorous comparisons are not possible because of the paucity of patients and differences in evaluation methods and patient characteristics, the demonstrated efficacy is not worse than those of oral drugs that are recommended as first-line agents (etretinate, cyclosporine) in the above-mentioned guidelines.[1]

Taking these considerations into account, Adacolumn is expected to be effective, even when used as first-line monotherapy in patients affected by conditions requiring systemic (oral) therapy with drugs such as etretinate and cyclosporine.

(6) The applicant set the duration of the prognosis study based on the therapeutic goal of maintaining approximately the same level of efficacy for 8 weeks (starting from the time

of evaluation) in patients who responded to the treatment with Adacolumn. This design was based on the 8-week dose interval for infliximab maintenance therapy, which was expected to be approved at the time the protocol of Adacolumn was being drawn up. Since the applicant evaluated efficacy at 2 weeks after the final apheresis treatment, the prognosis study was actually conducted 10 weeks after completion of the final apheresis treatment. In this clinical study, approximately the same level of efficacy was maintained for about 4 weeks in 1 patient and 8 weeks in 10 of the 11 patients in the prognosis study.

(7) Since the clinical study did not explore the re-treatment of patients who had previously been treated, the efficacy and safety of Adacolumn in re-treating pustular psoriasis have yet to be elucidated. The efficacy and safety of Adacolumn in re-treating pustular psoriasis will be investigated in the use-results survey.

(8) Pustular psoriasis can be classified as generalized pustular psoriasis characterized by multiple pustules over the whole body, or localized pustular psoriasis characterized by localized pustules that appear on parts of the body, mainly on the limbs. The applicant planned to investigate Adacolumn's efficacy and safety in the treatment of both types of the disease, but all 15 patients exhibited the generalized type. Thus, the applicant cannot discuss Adacolumn's efficacy and safety in patients with localized pustular psoriasis. However, as part of physicians' clinical research, a case report[3] has been published in which Adacolumn was used in a patient with localized pustular psoriasis who had failed to respond to oral etretinate and topical steroid/vitamin D_3. In this case, symptoms improved after the patient was treated with 2 sessions of apherasis, resulting in successful discontinuation of etretinate. While this is insufficient evidence, treatment of localized pustular psoriasis may be recommended in certain patients that fail to respond to existing systemic therapies and no other treatment is available.

Taking the applicant's responses into account, PMDA considers the clinical study results as follows:

Pustular psoriasis is a disease whose etiology has not yet been identified. The extent to which Adacolumn's mechanism of action in inhibiting inflammatory reactions contributes to improving pathological conditions, as described by the applicant, has yet to be fully elucidated.

Since the clinical study was an uncontrolled study that enrolled only 15 patients, rigorous verification of the usefulness of Adacolumn based on the resulting efficacy evaluation scores is difficult. Nevertheless, self-controlled comparisons of data collected before and after the treatment with Adacolumn are useful to some degree due to the carefully considered protocol, which incorporates various measures, including those to eliminate the influence of pharmacotherapies to the possible extent. Thus, the results demonstrate the efficacy of intervention with Adacolumn. For these reasons, the clinical study is valid for evaluating the efficacy of Adacolumn. On the other hand, intended use for Adacolumn should be carefully assessed because (a) enrolled patients in the clinical study were those who had failed to respond to pharmacotherapies, in order to eliminate the influence of pharmacotherapies; and (b) the number of patients for evaluating the efficacy and safety of Adacolumn was insufficient. Given the existence of patients with pustular psoriasis who had failed to respond to existing therapies or were ineligible for those therapies due to adverse drug reactions, as well as the treatment algorithm recommended in the above-mentioned treatment guidelines, PMDA considers it useful to allow Adacolumn to be used in clinical practice as a new option for treating pustular psoriasis, provided that the intended use reads "treatment of clinical symptoms of patients with moderate to severe pustular psoriasis who failed to respond to or are ineligible for existing oral systemic treatment." Some biological products (e.g., infliximab) have recently been indicated for the treatment of pustular psoriasis. While these biological products exhibit high clinical effectiveness,

they are associated with risk of infection or other serious adverse drug reactions, so only authorized institutions are allowed to use them. The revised Therapeutic Guidelines for Generalized Pustular Psoriasis, 2010 Edition[1] recommend careful use of the biological products in the primary care of systemic symptoms in the acute phase of the disease. In addition, the efficacy of Adacolumn in patients unresponsive to biological products was demonstrated in only 2 patients in the clinical study. Despite no safety issues, the number of patients is not necessarily sufficient to evaluate Adacolumn's clinical usefulness. Thus, it should be reminded that Adacolumn's efficacy and safety have not been fully evaluated in patients who had failed to respond to or were ineligible for biological products. At the same time, the investigation of these aspects should be prioritized in the use-results survey. The PRECAUTIONS section of the package insert should include an alert indicating that treatment with Adacolumn should be limited to 1 course (once a week for 5 weeks), with its therapeutic effects carefully monitored to prevent prolonged use of Adacolumn without careful consideration. This is because certain patients failed to respond to treatment with Adacolumn and these patients were classified as non-responders, and 1 such patient experienced aggravated symptoms. The relationship between the pathology of localized pustular psoriasis and generalized pustular psoriasis remains an open question. Nevertheless, it is acceptable to use Adacolumn to treat patients with localized pustular psoriasis who is deemed to be eligible for the treatment, since its treatment is similar to that of generalized pustular psoriasis,[4] and serious cases of localized pustular psoriasis have been reported in which existing therapies have been ineffective. The method for determining patient to which Adacolumn is applicable should be described in the package insert. The PRECAUTIONS section of the package insert should also include an alert stating that no established evidence exists with regard to the efficacy and safety of Adacolumn in the treatment of localized pustular psoriasis. Since the efficacy and safety of Adacolumn for such an intended use have not been established, it should be investigated in the use-results survey.

The duration of efficacy of Adacolumn and its efficacy and safety in repeat treatment were evaluated partially in the prognosis study of the clinical study, but the study was not necessarily adequate in this regard. Therefore, the investigation of these aspects should prioritized in the use-results survey.

Since the disease targeted by Adacolumn is rare and affects limited patients, PMDA considers it appropriate to register and monitor all patients in the use-results survey for a certain period until the planned number of patients (150) is enrolled.

IV. Results of Document-Based GCP Compliance Assessment

Based on the results of the document-based GCP compliance inspection, PMDA concluded that a regulatory review based on the submitted product application documents should pose no problems.

V. Overall Evaluation

Adacolumn is an adsorptive-type apheresis device developed to control excessive inflammatory reactions and to improve pathological conditions by removing granulocytes and other leukocytes from the peripheral blood via adsorption during the process of apheresis. The following were the key issues raised in the review of Adacolumn: (1) the validity of efficacy evaluations in an open-label, uncontrolled clinical study; (2) the intended use for Adacolumn; and (3) the efficacy and safety of Adacolumn when used to treat localized pustular psoriasis, and when used repeatedly or for an extended time. Taking into account the issues noted above and comments from the Expert Discussion, PMDA reached the following conclusion:

(1) Although the clinical study was not a controlled study, measures were taken to reduce bias, including establishing a pretreatment observation period and ensuring constant doses of concomitant drugs throughout the study period. The efficacy of Adacolumn can be evaluated based on a comprehensive assessment of several factors, including reduced severity scores and improvements in general patient condition. Despite the fact that the results of an investigation of such a small number of patients are not necessarily adequate for determining the clinical usefulness of Adacolumn, it would be useful to allow Adacolumn to be used in clinical practice as a new option for treating pustular psoriasis, given the existence of patients who failed to respond to or are ineligible for existing therapies or are ineligible for those therapies because of adverse drug reactions, as well as considering the treatment algorithm recommended in the above-mentioned treatment guidelines.

(2) Since many of the patients in the clinical study had failed to respond to existing therapies with oral drugs such as etretinate and cyclosporine, the intended use for Adacolumn should be "treatment of clinical symptoms of patients with moderate to severe pustular psoriasis who failed to respond to or are ineligible for existing oral systemic treatment." However, it should be reminded that Adacolumn's efficacy and safety have not been fully evaluated in patients who had failed to respond to or were ineligible for biological products. These aspects should be investigated in the use-results survey.

(3) Since the clinical study did not enroll any patients with localized pustular psoriasis, the study cannot establish the efficacy and safety of Adacolumn in such patients. Additionally, since the study assessed Adacolumn's efficacy for 10 weeks after treatment and did not investigate the duration of its efficacy for longer periods or the efficacy of repeated treatment, the duration of Adacolumn's efficacy in patients with pustular psoriasis and its efficacy and safety in repeated treatment remain unknown. Attention should be paid to the fact that Adacolumn's efficacy and safety have not been fully established for use in patients with localized pustular psoriasis, or for repeated or medium to long-term use. These aspects should be monitored for a certain period in the use-results survey.

Based on these results, PMDA has concluded that Adacolumn may be approved for the following intended use:

[Intended use]
Treatment of clinical symptoms of patients with moderate to severe pustular psoriasis for which existing oral systemic treatment have been ineffective or inapplicable.

Since Adacolumn is a new medical device and an orphan medical device, the appropriate re-examination period should be 7 years. Additionally, Adacolumn is not classified as a biological product or a specified biological product.

The application should be deliberated on at the Committee on Medical Devices and *In-vitro* Diagnostics.

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1 The Therapeutic Guidelines for Generalized Pustular Psoriasis 2010: Guidelines Incorporating TNF-α Inhibitor (Abridged). *The Japanese Journal of Dermatology*. 2010;120:815-839.

2 Wollina U, et al. Tumor Necrosis Factor-α Inhibitor-Induced Psoriasis or Psoriasiform Exanthemata. *American Journal of Clinical Dermatology*. 2008;9:1-14.

3 Seishima M, et al. Efficacy of Granulocyte and Monocyte Adsorption Apheresis for Pustular Psoriasis. *Therapeutic Apheresis and Dialysis*. 2008;12:13-18.

4 Nakanishi, et al. *The Japanese Journal of Dermatology*. 2009;119:873-879.