

LIXELLE®

β2-microglobulin Apheresis Column

Humanitarian Use Device

Authorized by Federal law for use in the treatment of patients with clinically-diagnosed dialysis-related amyloidosis (DRA).
The effectiveness of this device for this use has not been demonstrated.

Carefully review these Instructions for Use and use only under the direction of a licensed physician.

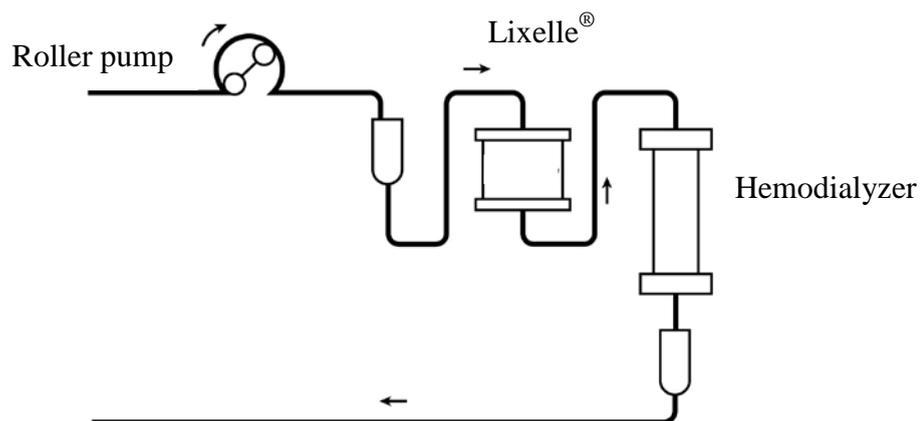
CAUTION: Federal (US) law restricts this device to sale by or on the order of a physician.

Manufactured by
KANEKA CORPORATION
Osaka, Japan

I. Introduction

The Lixelle® β 2-microglobulin apheresis column is an extracorporeal column for adsorption of β 2-microglobulin from circulating blood. It is used in conjunction with hemodialysis and is placed in series with a hemodialyzer in a hemodialysis circuit. The following diagram indicates the connection set up.

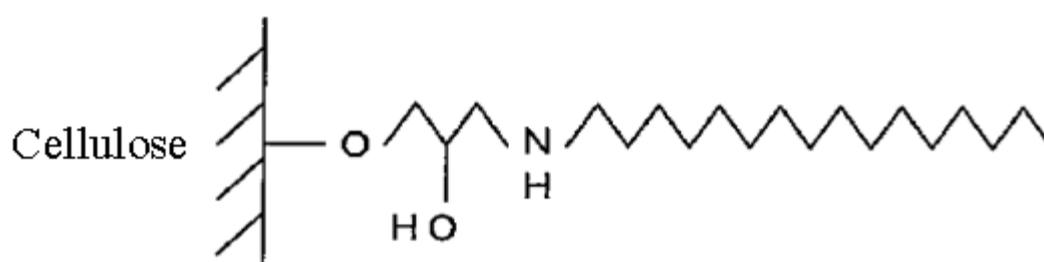
Figure 1: Lixelle® column in Hemodialysis blood circuit



Device Description

Lixelle® β 2-microglobulin (β 2m) Apheresis Column is an adsorbent column containing porous, spherical cellulose beads with covalently linked hexadecyl groups as ligands. The Lixelle® column adsorbs β 2m by the combined use of hydrophobic interaction and the appropriate pore size on cellulose beads. The beads contain a highly hydrophobic, covalently linked hexadecyl group, which is capable of binding the hydrophobic moiety of proteins. The size of the pores of the beads limits the size of the proteins and peptides adsorbed by the column to be between 4 and 20 kDa. It has been shown that the Lixelle® selectively binds β 2m (11.8 kDa), with a positive correlation between the amount of the β 2m adsorbed and the pretreatment serum β 2m level in both *in vitro* and clinical uses, while keeping essential proteins such as albumin (68 kDa) in the blood circulation. The structural formula is shown in Figure 2 below.

Figure 2: Structural formula of the ligand on Lixelle® beads.



The beads are packed in a column filled with sodium citrate solution as storage buffer and then sterilized. The Lixelle® column is supplied in three models: S-35 (350 ml capacity, 177 ml extracorporeal volume), S-25 (250 ml capacity, 105 ml extracorporeal volume), and S-15 (150 ml capacity, 65 ml extracorporeal volume).

Model	Column capacity (ml)	Extracorporeal Volume (ml)
S-15	150	65
S-25	250	105
S-35	350	177

II. Indications for Use

The Lixelle® β 2-microglobulin apheresis column is indicated for the treatment of patients with clinically-diagnosed dialysis-related amyloidosis (DRA).

III. Contraindications

The device is contraindicated for use in:

- (1) patients for whom adequate anticoagulation cannot be achieved, such as those with severe anemia, severe hemorrhagic diathesis, severe gastrointestinal ulcers, or who are receiving anticoagulant medications for any reason;
- (2) patients for whom extracorporeal circulation therapy is contraindicated, such as those with severe cardiac insufficiency, acute myocardial infarction, severe cardiac arrhythmia, acute seizure disorder, or severe uncontrolled hypertension or hypotension; and
- (3) patients with hypersensitivity to heparin or patients who have experienced hypersensitivity to the device.

IV. Special Patient Populations

The use of this device should be carefully considered in:

- (1) patients who are at a high risk of hypotension or who are of a small size because of the proportionally greater amount of extracorporeal volume used by the Lixelle® column;
- (2) pediatric patients, pregnant or breast-feeding patients, because no clinical data exist on its use in these patient populations and therefore the probable benefit or risks are unknown at this time;
- (3) patients with clotting disorders, because use of anticoagulant should be adjusted for patients with clotting disorders;
- (4) patients with severe liver function abnormalities, because no clinical data exist on its use in this patient population and therefore the probable benefit and risks are unknown at this time; and
- (5) patients with severe thyroid function disturbance, because no clinical data exist on its use in this patient population and therefore the probable benefit and risks are unknown at this time.

V. Warnings

- (1) The Lixelle® column should be used only according to these Instructions for Use and under the care of a physician experienced in hemodialysis. While connected to the extracorporeal system, the patient must be supervised at all times by a physician or qualified health care professional.

- (2) Rinse the Lixelle® column with at least 1000 mL of physiological saline solution at a flow rate of 50 to 150 mL/min and then, prime the Lixelle® column and the fluid pathway with at least 1000 mL of heparinized physiological saline solution, which should contain typically 1000 IU/L of heparin, at a flow rate of 50 to 150 mL/min. Rinsing is required to wash out the sodium citrate solution in the column to avoid the risk of citrate intoxication, and to mitigate potential safety hazards related to residual materials retained during device manufacturing.

The amount of heparin may be adjusted to the requirement of the individual patient by a supervising physician.

- (3) Use of an air-bubble detector with a clamp on the blood return line is mandatory to prevent air embolism, because air may be drawn into the extracorporeal circuit on the negative pressure side of the pumps. Blood returning to the patient must also be passed through the air bubble detector at all times.
- (4) The use of heparin for priming and for continuous injection is mandatory to prevent thrombus formation in the extracorporeal circuit. However, anticoagulation with too much heparin is associated with an increased bleeding risk, especially after treatment, and so puncture sites should be sufficiently compressed and cessation of bleeding should be confirmed.
- (5) In order to evaluate for potential safety hazards during treatment, patient vital signs should be monitored during treatment with the Lixelle® column. If any abnormality is observed, stop treatment or take appropriate action based on physician input.
- (6) The Lixelle® column should not be cleaned, reprocessed or resterilized and chemicals or solvents should not be used on the outside of the Lixelle® column.
- (7) For single use only. Do not reuse, reprocess or resterilize. Reuse, reprocessing or resterilization may compromise the structural integrity of the device and/or lead to device failure which, in turn, may result in patient injury, illness or death. Reuse, reprocessing or resterilization may also create a risk of contamination of the device and/or cause patient infection or crossinfection, including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to injury, illness or death of the patient.

VI. Precautions

- (1) To minimize the negative influence of substantial increases in extracorporeal volume in the first use of Lixelle®, use of smaller models (S-15 or S-25) in introduction period is recommended.
- (2) Treating physicians should consider withholding antihypertensive medications prior to the treatment in order to minimize the risk of hypotensive reactions during the extracorporeal therapy.
- (3) The Lixelle® column must not be operated above a maximum flow rate of 250 ml/min. There are no clinical data documenting the safe use of the device during hemodialysis at blood flow rates above 250 ml/min. Hemodialysis times should be adjusted for any patient undergoing treatment with the Lixelle® column so that an adequate Kt/V is maintained.
- (4) In terms of β_2 m adsorption capacity, the largest model, i.e., S-35 is recommended for use in the general patient population once a patient becomes accustomed to Lixelle® treatment. But, the relation between column size and efficacy has not been established. The smaller models, i.e., the S-15 and S-25 should be considered for patients who are at a high risk of hypotension or who are of a small size. It is recommended that the total extra corporeal whole blood volume (ECV) of Lixelle®

column, dialyzer and tubing should not exceed 10% of the patient's whole blood volume.

ECV calculation example

Lixelle®	Dialyzer	Tubing	Total	Minimum Weight
S-35 177ml	+ 120ml	+ 100ml	= 397ml	52kg
S-25 105ml	+ 120ml	+ 100ml	= 325ml	42kg
S-15 65ml	+ 120ml	+ 100ml	= 285ml	37kg

- (5) The smaller models, i.e., the S-15 and S-25 should be considered for patients with complications of hypotension or cardiac insufficiency, patients who require pressor drug administration during hemodialysis, or patients who have already experienced hypotensive reactions with the S-35.

Please note that using a smaller column may reduce the β_2 m clearance.

- (6) The Lixelle® column should be used in series with and upstream from a hemodialyzer, using connecting tubing compatible with the Lixelle® column. There are no clinical data documenting the safe use of the device during hemodialysis in alternate configurations.
- (7) Before use of the Lixelle® column, inspect all lines to ensure that they are not kinked or loosely connected. Lines that are occluded, or partially occluded, may lead to the procedure not operating correctly or to a fluid imbalance.
- (8) Relevant coagulation parameters, including the number of platelets and the coagulation studies or bleeding times, should be periodically reviewed (e.g., every 3 months) to ensure that the patient's blood coagulates appropriately.
- (9) Anemia has been observed in patients treated with the Lixelle® column. The etiology is not fully understood, however, available clinical data from a post-marketing study of Lixelle® conducted in Japan suggests that the possible cause is loss of blood due to blood clotting in the column, dialyzer or blood tubing. A study by Yamamoto et al., 2011 reported that the levels of serum iron did not change during the course of one year treatments of Lixelle®, and in vitro experiment has shown that free iron, ferritin, and transferrin are not adsorbed by Lixelle®. The amount of anticoagulant administered during Lixelle® treatment should be optimized for each patient to prevent anemia from blood clotting. Anemia is a very well-known adverse effect for hemodialysis patients. For patients on dialysis who are also treated with Lixelle®, the anemia should be treated in the same way as for patients on hemodialysis, following the clinical guidelines and FDA drug safety communications for the use of ESA.
- (10) The fluid pathway of the Lixelle® column is sterile and nonpyrogenic. Careful aseptic handling techniques are necessary to maintain this condition. Do not use the device if the package, the bag, or the product is damaged. Remove the device from the bag just before use.
- (11) Handle with care during transportation and storage. Keep the Lixelle® column in a clean place between 5 °C and 30 °C., Avoid direct sunlight, high humidity, excessive vibration and freezing conditions. Do not drop the Lixelle® column or strike it with a hard instrument (e.g., forceps). Do not use any Lixelle® column that has been damaged or frozen.
- (12) After use, dispose of product and packaging in accordance with hospital, administrative and/or relevant national regulations.

VII. Side Effects

- (1) Most of the adverse reactions are common for patients undergoing dialysis or any extracorporeal therapy, but combined usage with the Lixelle® column may increase the frequency at which these side effects occur. The most common (% of patients) side effects observed in the Japanese post-market (see Section IX below) safety study with the Lixelle® device were hypotension (14.2% of patients), anemia/decreased hematocrit (2.2-4.9%), hypovolemia (3.3%), nausea/vomiting (2.7%), fatigue/malaise (1.6%), palpitations (1.6%), chills/shivering (1.6%), and thrombocytopenia (1.1%). Other less frequently observed events (<1% of patients) included chest pain, dyspnea, increase of pain, hypertension after dialysis, abdominal pain, and pharyngeal pain. The most common adverse technical events during treatments included blood clotting in the Lixelle® column (4.4%), dialyzer (3.8%), and blood tubing (2.7%). Of note, in one of the subsequent clinical studies [(Section IX: Study by Gejyo, et al. (2004)], higher proportions of hypotension (27.3% of patients) and anemia (18.2%) were observed. In general, these reactions are manageable through discontinuation of the treatment and/or appropriate medical intervention by the attending physician.
- (2) Given that the Lixelle® column is an extracorporeal therapy, other potential side effects include cardiac dysrhythmia, muscle cramping, itching, headache, dizziness/fainting, hemolysis, and hematoma formation at the venipuncture site. Compared with hemodialysis therapy alone, the increased extracorporeal fluid volume required for Lixelle® can potentially lead to a greater risk of hypotension, hypovolemia, clotting, and blood loss. Additionally, there are additional tubing connections which increase handling and the risk of contamination and potential for infection. There is also the possibility of allergic or hypersensitivity reactions given that patients are exposed to additional biomaterials. The addition of the Lixelle® column to the extracorporeal circuit also increases the potential for removal of beneficial substances from the blood.
- (3) As shown in the table below, in addition to β 2-microglobulin, other substances (Gastrin, ACTH, Insulin, Osteocalcin, PTH, Lysozyme, Myoglobin, etc.) are adsorbed by the Lixelle® column. Clinicians should carefully monitor blood chemistries for any clinically significant changes.

Blood components showing adsorption rates of >20% by Lixelle® beads (*in vitro*†)

	Concentration (average of 3 runs)		Adsorption Rate (100 - after/before x 100)
	Before	After	
β 2-microglobulin (mg/L) *	35	0.58	98 %
Gastrin (pg/mL)	140	30	79 %
ACTH (pg/mL)	34	5.3	84 %
Insulin (μ U/mL) *	49	3.5	93 %
Osteocalcin (ng/mL)	5.9	1.0	83 %
PTH-intact (pg/mL)	29	12	59 %
Lysozyme (μ g/mL) *	66	1.8	97 %
Myoglobin (ng/mL) *	120	5.3	96 %
Total bile acids (μ mol/L) *	3.7	0.5	86 %
Retinol binding protein (mg/dL) *	15	10	32 %
Folic acid (ng/mL)	5.6	4.4	22 %
TSH (μ U/mL)	1.5	1.0	32 %
ADH (pg/mL)	3.6	2.9	20 %
Pancreatic glucagon (pg/mL)	107	75	30 %
Secretin (pg/mL)	107	75	30 %
Calcitonin (pg/mL)	21	15	30 %
Aldsteron (pg/mL)	60	42	30 %
Progesterone (ng/mL)	6.5	4.6	30 %

Estradiol (pg/mL)	129	87.7	32 %
Total protein (g/dL) *	6.0	5.9	2 %
Albumin (g/dL) *	2.8	2.8	0 %

† These data showing adsorption rates of 20 % or greater, total protein and albumin from selectivity testing of Lixelle® beads *in vitro*. 6 ml of the serum of healthy humans or a dialysis patient was mixed with 1 ml of adsorbent and shaken for 2 hours in an incubator at 37 °C. The supernatant was collected and analyzed. Levels before adsorption were determined in the same manner, except that 0.5 ml of isotonic saline was used instead of the adsorbent. (data from the article; Nakatani M, Furuyoshi S, Takata S, Tani N. Adsorption Characteristics of the Direct Hemoperfusion Column “Lixelle” for the Treatment of Dialysis-Related Amyloidosis. *Jpn J Artif Organs*. 1998; 27(2), 571-577..

* The results using serum of a dialysis patient, which has very high levels of these blood components.

Changes of blood substances including blood cells in each session between hemodialysis (HD) and HD + Lixelle® S-35 (the largest model) (clinical data†)

(1) Data from the article; Gejyo, *et al.* *Kidney and Dialysis*. 37(4), 749-756, 1994.

Test item	Only hemodialysis			HD + Lixelle®			n
	Before treatment	After treatment	% change	Before treatment	After treatment	% change	
BUN (mg/dL)	73.4 ± 19.1	26.5 ± 9.6	35.8 ± 8.5	75.2 ± 18.0	27.4 ± 8.8	36.3 ± 6.6	19
Creatinine (mg/dL)	11.7 ± 3.7	5.0 ± 1.9	42.6 ± 8.0	11.7 ± 3.5	5.0 ± 1.9	41.9 ± 7.5	19
Uric acid (mg/dL)	7.3 ± 1.6	2.4 ± 0.8	33.8 ± 8.1	7.2 ± 1.4	2.4 ± 0.7	33.7 ± 6.6	19
Na (mEq/L)	138.5 ± 3.7	143.1 ± 8.9	103.3 ± 6.4	139.4 ± 2.5	141.6 ± 2.2	101.7 ± 1.8	19
K (mEq/L)	5.1 ± 0.7	3.4 ± 0.3	68.1 ± 6.4	5.1 ± 0.7	3.4 ± 0.3	68.0 ± 6.0	19
Cl (mEq/L)	101.1 ± 3.6	100.8 ± 4.0	99.8 ± 5.1	101.9 ± 3.2	102.6 ± 1.9	100.7 ± 3.2	19
Ca (mEq/L)	4.7 ± 0.5	5.1 ± 0.5	107.3 ± 7.9	4.8 ± 0.4	4.9 ± 0.4	103.3 ± 7.7	18
IP (mg/dL)	5.8 ± 1.5	3.0 ± 0.7	52.7 ± 10.8	5.4 ± 1.3	2.7 ± 0.5	51.6 ± 11.4	19
Mg (mg/dL)	2.7 ± 0.4	2.1 ± 0.2	80.8 ± 8.0	2.7 ± 0.4	2.1 ± 0.2	78.9 ± 7.7	18
Fe (µg/dL)	56.0 ± 18.1	72.2 ± 27.4	132.4 ± 39.5	58.6 ± 15.0	109.7 ± 34.5	250.8 ± 216.6	18*
Cholesterol (mg/dL)	160.6 ± 50.0	191.5 ± 66.2	118.5 ± 14.0	160.3 ± 45.3	180.0 ± 56.6	111.6 ± 12.7	19**
Total protein (g/dL)	6.4 ± 0.4	7.5 ± 1.1	117.5 ± 14.1	6.4 ± 0.4	7.2 ± 0.9	112.5 ± 11.9	19**
Albumin (g/dL)	3.6 ± 0.4	4.2 ± 0.8	116.1 ± 14.9	3.6 ± 0.4	4.1 ± 0.7	111.8 ± 11.9	19*
A/G ratio	1.9 ± 0.3	1.8 ± 0.3	97.6 ± 4.5	1.9 ± 0.3	1.9 ± 0.3	101.5 ± 4.9	23**
Albumin (%)	64.9 ± 4.2	64.3 ± 4.1	99.1 ± 1.7	64.8 ± 4.5	65.0 ± 3.9	100.5 ± 1.8	23**
α 1 (%)	3.2 ± 0.7	3.2 ± 0.8	99.3 ± 13.6	3.5 ± 0.4	3.3 ± 0.7	95.6 ± 13.5	23
α 2 (%)	8.3 ± 1.5	8.2 ± 1.5	98.6 ± 7.9	8.2 ± 1.2	8.1 ± 1.2	97.7 ± 3.8	23
β (%)	7.6 ± 1.0	8.3 ± 1.4	110.3 ± 18.5	7.7 ± 0.9	8.1 ± 1.4	105.3 ± 13.2	23
γ (%)	16.0 ± 4.2	16.0 ± 4.2	100.6 ± 8.8	15.8 ± 4.2	15.5 ± 4.1	98.0 ± 5.7	23
Total bilirubin (mg/dL)	0.3 ± 0.1	0.4 ± 0.1	149.1 ± 65.8	0.2 ± 0.1	0.4 ± 0.2	198.5 ± 100.4	19*
TTT (U)	3.5 ± 2.6	4.3 ± 3.2	130.8 ± 59.2	3.8 ± 2.6	3.7 ± 2.8	101.7 ± 38.0	19
ZTT (U)	9.9 ± 5.0	9.2 ± 5.2	95.8 ± 25.9	9.4 ± 4.6	9.2 ± 4.5	99.6 ± 11.3	19
GOT (U/L)	19.6 ± 8.6	22.2 ± 7.9	119.9 ± 25.2	27.0 ± 27.6	25.0 ± 12.3	107.7 ± 20.5	19*
GPT (U/L)	13.5 ± 8.4	16.0 ± 9.4	127.3 ± 54.7	15.5 ± 9.7	16.2 ± 9.9	110.7 ± 24.4	19
ALP (U/L)	153.8 ± 92.4	174.4 ± 93.5	115.6 ± 13.0	157.8 ± 100.4	170.7 ± 90.5	111.3 ± 13.4	18*
LDH (U/L)	318.7 ± 84.3	363.4 ± 87.3	116.5 ± 23.4	319.9 ± 79.6	359.4 ± 61.8	115.1 ± 20.4	19
γ-GTP (U/L)	18.6 ± 12.5	21.6 ± 13.2	119.5 ± 16.5	20.6 ± 15.1	22.4 ± 14.6	113.5 ± 13.7	19*
LAP (U/L)	42.9 ± 15.4	46.3 ± 18.3	110.3 ± 29.2	42.8 ± 16.5	45.7 ± 13.2	111.5 ± 18.1	19
Ch-E (U/L)	2470.3 ± 833.1	2927.3 ± 1068.2	117.6 ± 15.3	2486.5 ± 850.4	2814.5 ± 995.8	112.4 ± 13.7	19*
CPK (U/L)	57.2 ± 33.6	56.2 ± 41.1	94.1 ± 18.7	66.8 ± 49.5	57.4 ± 48.9	81.9 ± 16.6	19**
CRP (mg/dL)	0.4 ± 0.1	0.4 ± 0.2	126.1 ± 74.6	0.4 ± 0.1	0.4 ± 0.1	132.3 ± 80.7	14
β2-MG (mg/L)	33.9 ± 8.6	20.0 ± 7.0	58.6 ± 12.7	32.0 ± 9.9	9.0 ± 3.2	28.2 ± 4.9	19**
T ₃ (ng/dL)	94.8 ± 19.2	127.2 ± 38.4	134.0 ± 31.5	96.9 ± 19.6	117.8 ± 41.1	120.3 ± 30.7	17*
T ₄ (µg/dL)	7.5 ± 1.4	9.3 ± 1.6	124.8 ± 17.7	7.8 ± 1.9	8.9 ± 1.5	118.7 ± 22.8	17
Aldosterone (ng/dL)	50.7 ± 117.1	53.4 ± 122.7	104.8 ± 50.1	36.3 ± 73.5	60.3 ± 135.1	125.0 ± 78.9	9
c-PTH (ng/mL)	5.5 ± 4.5	3.2 ± 3.0	63.1 ± 20.7	5.7 ± 4.7	2.5 ± 2.3	53.5 ± 22.4	19*
IRI (µU/mL)	17.6 ± 11.5	33.8 ± 25.2	246.0 ± 193.8	22.8 ± 18.8	28.4 ± 16.5	233.2 ± 232.7	17
Cortisol (µg/dL)	10.8 ± 2.5	11.6 ± 3.7	109.9 ± 31.5	11.0 ± 2.0	14.0 ± 4.7	140.1 ± 64.9	20*
C3 (mg/dL)	63.1 ± 12.7	71.9 ± 18.4	114.0 ± 18.8	63.8 ± 12.5	64.8 ± 15.6	102.3 ± 16.7	17**
C4 (mg/dL)	30.8 ± 7.1	36.5 ± 10.7	118.0 ± 15.0	31.0 ± 7.4	33.5 ± 9.9	109.8 ± 13.8	17**
C5 (mg/dL)	11.3 ± 3.0	14.3 ± 4.2	129.2 ± 31.8	10.8 ± 2.6	12.4 ± 3.2	118.2 ± 24.9	22
CH ₅₀ (U/mL)	22.3 ± 7.3	30.0 ± 9.2	141.4 ± 46.0	24.8 ± 6.7	29.2 ± 7.8	122.9 ± 40.8	21

RBP (mg/dL)	15.0 ± 3.7	16.0 ± 4.7	106.0 ± 14.2	14.5 ± 3.2	12.2 ± 4.2	82.6 ± 16.0	21**
Lysozyme (mg/L)	40.5 ± 6.4	21.6 ± 10.6	53.0 ± 24.0	39.9 ± 7.0	13.2 ± 3.6	33.0 ± 9.2	16**
Prolactin (ng/mL)	27.8 ± 42.1	21.0 ± 29.8	80.1 ± 19.8	29.0 ± 48.6	11.6 ± 19.7	41.8 ± 9.8	17**
IgG (mg/dL)	1431.6 ± 331.7	1696.7 ± 354.9	119.8 ± 16.9	1440.2 ± 330.0	1576.9 ± 309.7	112.3 ± 14.5	16*
IgA (mg/dL)	218.5 ± 67.4	249.4 ± 75.4	114.5 ± 11.7	213.4 ± 65.9	232.4 ± 74.6	109.0 ± 13.6	16*
IgM (mg/dL)	196.7 ± 73.9	233.5 ± 96.6	119.2 ± 16.5	195.5 ± 70.8	216.2 ± 92.0	111.1 ± 15.3	15**
HS-PTH (pg/mL)	16726.1 ± 13989.3	9148.5 ± 8708.5	57.0 ± 14.8	17854.2 ± 16660.0	7014.6 ± 6848.1	44.1 ± 12.1	24
WBC (/mm ³)	4425.0 ± 1443.5	4383.3 ± 1551.3	98.9 ± 12.8	4729.9 ± 1099.7	3993.8 ± 1675.9	87.8 ± 35.3	24
RBC (10 ⁴ /mm ³)	304.5 ± 59.9	342.7 ± 81.8	119.9 ± 10.3	290.3 ± 54.4	317.5 ± 76.6	108.9 ± 9.9	24
Hb (g/dL)	9.3 ± 1.7	10.4 ± 2.3	111.5 ± 10.1	8.8 ± 1.5	9.6 ± 2.2	108.9 ± 9.9	24
Hct (%)	28.6 ± 5.6	32.4 ± 7.7	112.6 ± 11.1	27.3 ± 4.9	30.0 ± 6.9	109.6 ± 9.7	24
MCV (μ ³)	94.1 ± 6.5	94.6 ± 6.7	100.5 ± 1.8	94.3 ± 6.5	94.8 ± 6.5	100.3 ± 0.9	24
MCH (μg)	30.6 ± 2.6	30.5 ± 2.5	99.7 ± 1.7	30.5 ± 2.4	30.5 ± 2.4	100.0 ± 1.1	24
MCHC (%)	32.5 ± 1.4	32.2 ± 1.2	99.2 ± 2.5	32.4 ± 0.9	32.2 ± 0.9	99.6 ± 1.4	24
Plt (10 ⁴ /mm ³)	14.7 ± 5.3	16.5 ± 6.4	111.2 ± 15.5	15.1 ± 4.9	15.3 ± 5.4	101.6 ± 16.4	24**

Paired-t test; * $p < 0.05$, ** $p < 0.01$ (2) Data from the article; Nakazawa, *et al.* Int J Artif Organs. 16(12), 823-829, 1993.

Test item	Method	HD	HD + Lixelle®	n	p
β2-MG (mg/L)	RIA	55.0 ± 8.0	27.1 ± 4.8	20	< 0.01
RBP (mg/L)	SRID	107.5 ± 14.1	86.2 ± 13.3	18	< 0.01
Lysozyme (mg/L)	Turbidimetry	46.8 ± 21.9	30.5 ± 8.2	16	< 0.01
Prolactin (ng/mL)	RIA	78.3 ± 21.3	40.6 ± 10.4	19	< 0.01
c-PTH (ng/mL)	RIA	56.0 ± 17.0	47.7 ± 20.4	16	
HS-PTH (pg/mL)	RIA	52.5 ± 11.9	41.8 ± 12.1	20	< 0.01
IRI (μU/mL)	RIA	274.7 ± 200.6	269.9 ± 241.6	19	
WBC (/mm ³)	Coulter	101.8 ± 11.3	88.0 ± 37.0	20	
RBC (10 ⁴ /mm ³)	Coulter	115.1 ± 8.8	111.2 ± 8.0	20	< 0.05
Hb (g/dL)	Coulter	114.5 ± 8.7	111.0 ± 7.9	20	< 0.05
Hct (%)	Coulter	118.1 ± 9.6	111.8 ± 7.9	20	< 0.05
Plt (10 ⁴ /mm ³)	Coulter	115.0 ± 14.6	106.1 ± 15.0	20	< 0.05

RIA = radioimmunoassay, SRID = single radial immunodiffusion, Coulter = coulter counter

These clinical data demonstrate the following;

- The measured test values showed some changes compared to those for dialysis alone, but the changes were not considered to be clinically significant and no adverse effects were observed.
- The obvious increase of Fe observed in HD + Lixelle® is probably due to preventive administration of iron during the session for some patients with declining tendency of hematocrit.
- The adsorption data obtained in clinical studies using Lixelle® S-35 (the largest model) suggest that the adsorption of blood substances by Lixelle® is not clinically significant, and the smaller models with less adsorptive capacity are similarly regarded as safe.

VIII. Instructions for operation

The Lixelle® column should be used in series with and upstream from a hemodialyzer, using connecting tubes with luer lock connectors. The Lixelle® column must not be connected downstream of the hemodialyzer.

Since the connector of Lixelle® is designed to comply with ISO 8637, please make sure that the tubing connector with which Lixelle® is connected complies with ISO 8638.

The tubing set(s), hemodialyzer and hemodialysis machine should be operated in accordance with their respective Instruction for Use.

(1) Rinsing and priming

- Fill the arterial line of the dialysis blood tubing set with the physiological saline solution.

- (ii) Connect the Lixelle® column to the arterial line of the dialysis blood tubing set. (Do not allow air bubbles to enter the tubing set or the Lixelle® column.)
- (iii) Connect the connecting tubing to the downstream side of the Lixelle® column.
- (iv) Fill the connecting tubing with the physiological saline solution.
- (v) Connect the hemodialyzer to the connecting tubing, and connect the hemodialyzer to the venous line of the dialysis blood tubing set.
- (vi) Rinsing of Lixelle® column: Rinse the Lixelle® column, hemodialyzer, blood tubing set and connecting tubing (hereunder “the System”) using at least 1000 mL of physiological saline solution at a flow rate of 50 to 150 mL/min.
- (vii) Rinsing of the other components: Rinse the entire System again in accordance with instructions for use of each component provided by each manufacturer.
- (viii) Priming of the System: Prime the entire System at least 1000 mL of heparinized physiological saline solution, which should contain typically 1000 IU/L of heparin, at a flow rate of 50 to 150 mL/min. The amount of heparin may be adjusted to the requirement of the individual patient by a supervising physician.

(2) Treatment

- (i) Connect the arterial line and the venous line to the patient.
- (ii) Start the operation of the circuit at a blood flow rate of 100 to 250 mL/min, continuously infusing 1,000 ~ 1,500 IU/hr of heparin. The flow rate and dosage of heparin should be determined by the physician based on the patient’s overall condition. The Lixelle® column must be operated at a maximum flow rate of 250 ml/min.
- (iii) The amount of anticoagulant administered during Lixelle® treatment should be optimized for each patient to prevent anemia from blood clotting.
- (iv) Closely monitor patient clotting time periodically during the procedure to ensure that an adequate level of anticoagulation is maintained.

(3) After treatment

- (i) After completion of the treatment, return the blood remaining in the Lixelle® column, the hemodialyzer and the tubing lines to the patient using 150 to 200 mL of physiological saline solution at a flow rate of approximately 50 mL/min.
- (ii) Disconnect the circuit from the patient and dispose of the Lixelle® column and other components in accordance with hospital, administrative and/or relevant national regulations.

IX. Clinical Experience

The Lixelle® column has been studied in numerous small clinical trials with results published in the literature. These articles describe the treatment of approximately 100 patients with DRA in Japan. The four key studies that support the safety and probable benefit of the Lixelle® column are described in the section below.

Study by Gejyo, et al. (2004)¹

This was a 2 year, prospective, randomized, controlled study of 44 subjects who were randomized 1:1 to either hemodialysis alone (control group) or hemodialysis plus the

¹ Gejyo F, Kawaguchi Y, Hara S. Arresting Dialysis related amyloidosis: a prospective, multicenter controlled trial of direct hemoperfusion with a β 2-microglobulin adsorption column. *Artif. Organs.* 2004; 28(4): 371-380.

Lixelle® (S-35) β 2m apheresis column (Lixelle® group). Long-term dialysis patients were enrolled who had one of the following: (a) synovial membrane biopsy sample obtained during surgery for carpal tunnel syndrome, (b) immuno-histochemically demonstrated deposition of β 2m amyloid fibrils, or (c) radiographic or computed tomography (CT) findings of bone cysts in a hand (2 mm or greater diameter) or other joints (5 mm or greater diameter). All subjects were treated with a high-flux polysulfone hemodialyzer (Kawasumi Laboratories PS series) during their hemodialysis sessions, and both groups were treated for a total of 2 years.

Removal of β 2m was determined from blood samples obtained once per month immediately before and immediately after dialysis, and serum β 2m concentrations were measured by radioimmunoassay. β 2m removal rate and plasma β 2m clearance were calculated.

Joint pain was evaluated once a month using a four point (0-3) grading scale. Evaluation of pain was performed three (3) times (on the day of dialysis treatment, during the daytime and at night on the day following dialysis treatment) for neck, shoulders, elbows, hands, fingers, knees, legs, and feet. The sum of the scores obtained in the three (3) times evaluation for each joint was used for the analysis.

Activities of daily living were assessed monthly using a questionnaire that was developed by the Neuro-Muscular Rehabilitation Study Group of the Japanese Ministry of Health and Welfare. The questionnaire assessed activities such as eating, dressing, bathing, toileting, and personal grooming.

Degree of stiffness was assessed every three months for shoulders, elbows, joints of the hands, hip joints, knees, legs, feet, and joints of the neck, according to a 4 point grading scale. The sum of the scores was used for analysis. Subjects were also asked about degree of morning stiffness and frequency of nighttime awakening.

Osteolucency was evaluated every 6 months on radiographs of the joints and spine. A bone cyst involving the hand joint was diagnosed when it was greater than 2 mm in diameter, while other cysts were diagnosed when they were greater than 5 mm. The presence and number of bone cysts were assessed by two physicians who were blinded to the subjects' background and treatment.

Results

Data demonstrating probable benefit were reported for 18 subjects in each group. Four (4) of the 22 treatment subjects enrolled were excluded from the Lixelle® group due to discontinuation as a result of adverse events.

Blood samples obtained at the beginning and end of the first treatment showed serum β 2m reductions that were greater in the Lixelle® group ($74.1 \pm 6.1\%$) compared to the control group ($60.1 \pm 6.3\%$), while β 2m plasma clearances were 80.9 ± 9.9 mL/min for the Lixelle® group and 52.3 ± 23.3 mL/min for the control group.

The clinical outcomes (ADL, pain, and stiffness) improved in the Lixelle® group between the first and last treatments, while no improvement was seen in the control group.

The "grip strength test" was used to measure the grasping power of each hand. At the end of the two year study period, the control group continued to show a decline in grasp strength from 16.3 ± 10.9 kg to 14.0 ± 11.4 kg for the left hand and from 17.5 ± 11.0 kg to 15.3 ± 10.4 kg for the right hand, respectively. Conversely, the Lixelle® group showed maintenance of the grasping strength, from 13.9 ± 8.4 to 14.6 ± 9.0 kg for the left hand and from 16.9 ± 10.5 kg to 16.6 ± 9.7 kg for the right hand.

Radiographs showed that the number of joints with bone cysts increased for the control group compared to baseline, while no change was observed for the Lixelle® group.

Of the 22 subjects in the Lixelle® group, 11 subjects reported adverse events. Six (6) subjects (27.3%) developed hypotension, 4 subjects (18.2%) developed anemia with a decrease in hematocrit and 1 subject (4.5%) developed pharyngeal pain. Lixelle® treatment was discontinued for 6 of the above subjects, i.e., 2 of the 6 who developed hypotension, 3 of the 4 who developed anemia, and the one subject who developed pharyngeal pain.

The author indicated that the development of hypotension was attributable to an increase in extracorporeal blood volume, and that the anemia may have been due to the trapping of residual blood in the Lixelle® column and/or dialyzer after treatment. No cause of pharyngeal pain is suggested.

The study limitations include the small number of subjects and that the subjective outcomes (pain, stiffness, ADLs) were assessed without blinding the subjects or investigators. Additionally, it is unclear whether the observed differences in grip strength and bone cysts are clinically significant. The reported safety outcomes are descriptive at best, given that adverse events were not systematically assessed, and safety outcomes were not compared with the control group.

Summary

This study was a prospective, randomized trial of 44 subjects with DRA, randomized 1:1 to Lixelle® plus hemodialysis or hemodialysis alone. Subjects were treated for a total of two years. The results show:

- Greater removal of β_2m during each treatment for subjects in the Lixelle® group compared to subjects who received hemodialysis alone;
- Improvements in subjective measures, such as pain, stiffness and ADL were seen for the Lixelle® group but not for the control group;
- Worsening of objective measures such as hand grasping strength and the number of bone cysts was observed in the control group and no changes in these measures were observed for the Lixelle® group.
- Adverse events observed in this study were hypotension, anemia and pain.

Study by Abe, et al. (2003)²

This was a prospective, two-year study of 17 subjects with DRA in which subjects served as their own control. Subjects were treated for one year with high flux dialysis alone, followed by one year of treatment with high flux dialysis and the Lixelle® β_2m apheresis column (S-35). During the study period, both subjective (joint pain and activities of daily living) and objective (pinch strength, motor terminal latency, β_2m levels) were measured.

Twenty two (22) subjects were enrolled. The inclusion criteria were (1) the presence of tissue deposition of amyloid with β_2m confirmed by surgery or biopsy; (2) patient had been receiving dialysis for a minimum of 10 years; (3) patient had undergone carpal tunnel surgery; (4) bone cysts detected by radiographic imaging.

² Abe T., Uchita K., Orita H. Effect of β_2 -microglobulin adsorption column on dialysis-related amyloidosis. *Kidney Int.* 2003; 64:1522-28.

Five subjects dropped out of the study. Four (4) subjects voluntarily withdrew and one subject was transferred to another hospital for surgery. During Year 1, subjects were treated for 4 hours three times a week by high flux dialysis, and this dialysis schedule remained unchanged during Year 2 (when the Lixelle® β 2m apheresis column was also used).

Objective measurements included tip pinch strength, and median motor terminal latency which was performed on the median and ulnar nerves.

Subjective measures included the Activities of Daily Living (ADL) score as assessed by the modified Health Assessment Questionnaire (m-HAQ) questionnaire,³ and joint pain, which was assessed using a validated 10 cm Visual Analog Scale (VAS) that has been widely used in pain studies.⁴ Pain was assessed in the shoulder, elbow, wrist, finger, coxa, knee and foot. Frequency of nocturnal awakening from pain was also assessed with the VAS.

Results

At the start of Year 1, the β 2m level was 34.6 ± 9.3 mg/L and remained unchanged over the year treatment period (34.5 ± 8.4 mg/L). However, over Year 2, the β 2m level decreased to 28.8 ± 7.3 mg/L. Consistent with other studies, this study showed that the average change in β 2m concentration in one Lixelle® treatment was a $74 \pm 6\%$ reduction.

Pinch strength improved with Lixelle® β 2m apheresis column treatment, increasing from 6.8 ± 4.7 lbs at the end of Year 1 to 9.1 ± 5.5 lbs at the end of Year 2. The final strengths approach the normal age-matched range for these subjects.

At the end of Year 2, the median motor terminal latency was reduced, but the ulnar motor terminal latency was not changed. The median nerve, unlike the ulnar nerve, passes through a tight tunnel, and β 2m deposits can cause compression of this nerve leading to carpal tunnel syndrome.

Improvements in joint pain (VAS) were noted, declining from 5.7 ± 2.1 at the end of Year 1 to 4.1 ± 2.4 at the end of Year 2. Frequency of nocturnal awakenings also decreased. With regard to the ADL, decreases in the mHAQ ADL score were noted for activities related to the upper extremities (dressing and grooming, eating, maintaining hygiene, reaching and gripping) with Lixelle® treatment. No differences were noted for ADL related to the lower extremities (arising, walking, and other activities). The authors speculate that activities related to the lower extremities may take longer to show improvement.

The authors note that there were no incidents of hypotension or anemia.

The limitations of this study are the small number of subjects and the lack of a randomized control group. Another limitation is that the subjective outcomes (pain, nocturnal awakening, ADLs) were assessed without blinding the subjects or investigators. Additionally, it is unclear whether the observed differences in pinch strength and median motor terminal latency are clinically significant, although improvement in upper extremity ADLs were noted. No hypotension or anemia was reported, but it is not clear if safety was systematically assessed in the study.

³Pincus T, Summey JA, Soraci SA Jr, Wallston KA, Hummon NP. Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. *Arthritis Rheum.* 1983 Nov; 26(11): 1346-1353.

⁴Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. *J Clin Nurs.* 2005 Aug; 14 (7): 798-804..

Summary

This study was a prospective trial of 17 subjects with DRA. Subjects served as their own controls and were treated for a total of two years; Year 1 with dialysis alone followed by Year 2 of dialysis plus the Lixelle® β 2m apheresis column. The results show:

- Reductions in serum β 2m for subjects in the Lixelle® group after 12 months of therapy compared to no change during Year 1 (dialysis alone);
- Improvements in subjective measures, such as pain and ADL were observed during Year 2 (treatment with the Lixelle® β 2m apheresis column);
- Improvements were seen during Year 2 for objective measures such as hand pinch strength and median motor terminal latency;
- Hypotension and anemia were not observed.

Study by Yamamoto et al. (2011)⁵

This was a 2-year study that enrolled 20 subjects. Subjects suffered from DRA with chronic renal failure and fulfilled the following inclusion criteria: (1) Proven presence of tissue deposition of amyloid with β 2m confirmed by surgery or biopsy; (2) dialysis for at least 10 years and had undergone carpal tunnel surgery; (3) bone cysts detected by radiographic imaging.

Treatment with Lixelle® was conducted three times per week. Only the Lixelle® S-15 device was used. During Year 1, the subjects received only dialysis while in Year 2, subjects received dialysis plus the Lixelle® β 2m apheresis column. Subjects served as their own controls.

Joint pain (severity and frequency of nocturnal awakening) was assessed using a standard 10 cm VAS scale, which is widely used and has been validated for assessment of pain.⁴ Activities of daily living scores were assessed using a modified Health Assessment Questionnaire (mHAQ).³ Pinch strength was assessed using pinch gauge with standardized limb positioning. Levels of β 2m were measured by blood sampling before dialysis and were examined for changes every six months.

Adverse events were collected, along with changes in hemoglobin (Hb) and hematocrit (Hct), and the need for erythropoietin.

Results

Three of the 20 enrolled subjects dropped out of the study. One subject died three months after the start of the study with severe cardiovascular disease, and two subjects withdrew.

The ADL score and VAS pain improved over the 12 months of the Lixelle® β 2m apheresis column treatment. VAS pain decreased from 5.0 ± 1.9 at the beginning of the Lixelle® treatment to 3.2 ± 2.3 at 12 months. The ADL scores also improved, from 0.96 ± 0.56 to 0.52 ± 0.40 at the end of twelve months. Pinch strength improved from 5.9 ± 3.0 lbs at the beginning of treatment to 7.2 ± 3.2 lbs at the end of 12 months treatment with the Lixelle® β 2m apheresis column. This change brings subjects closer to the normal, age-matched range for this test, which is 11.4 to 18.3 lbs.

⁵ Yamamoto, Y., Hirawa N., Yamaguchi S., Ogawa N., Takeda H., Shibuya K., Kawahara K., Kojima H., Dobashi Y., Fujita M., Azusima K., Miyazaki N., Kobayashi M., Kobayashi C., Fujiwara A., Yuto J., Saka S., Yatsu, K., Toya Y., Yasuda G., Ohnishi T., Umemura S. Long term efficacy and safety of the small-sized β 2-microglobulin adsorption column for dialysis-related amyloidosis. *Therap. Apheresis Dialy.*; 2011; 15(5): 466-474.

The β 2m levels decreased from 29.3 ± 9.6 mg/L to 24.7 ± 5.1 mg/L after 12 months of Lixelle® β 2m apheresis column usage.

No adverse events, such as hypotension or anemia, were observed. The dose of erythropoietin did not change.

The limitations of this study are the small number of subjects and the lack of a randomized control group. Another limitation is that the subjective outcomes (pain, ADLs) were assessed without blinding the subjects or investigators. Additionally, it is unclear whether the observed differences in pinch strength are clinically significant. The authors also noted that this was a smaller population (mean body mass index of 19.7), so it may not be possible to generalize the results to subjects with larger body mass. No adverse events were observed, but it is not clear if safety was systematically assessed in the study.

Summary

This study was a prospective trial of 17 subjects with DRA using the smaller Lixelle® S-15 device. Subjects served as their own controls and were treated for a total of two (2) years; Year 1 with dialysis alone followed by Year 2 of dialysis plus the Lixelle® β 2m apheresis column. The results show improvements in both objective and subjective measures:

- Reductions in serum β 2m after 12 months of therapy;
- Improvements in subjective measures, such as pain and ADL;
- Improvements for objective measures such as hand pinch strength
- Hypotension and anemia were not observed, and the erythropoietin dose did not change.

Study by Kuragano et al. (2011)⁶

This was a prospective, multi-center study of 39 subjects treated with the Lixelle® β 2m apheresis column for a period of 1 year. Subjects were included, if they were long-term dialysis patients, and if they had clinical manifestations of DRA including evidence of bone cysts. A retrospective control group of 26 subjects was also included, and consisted of patients who had undergone long-term hemodialysis (HD) and had bone cysts but did not complain of symptoms of DRA.

Patients were excluded if they had severe cardiovascular disease, infectious disease, malignant tumors, diabetes mellitus, severe anemia or hypotension. The same inclusion/exclusion criteria were applied to the retrospective control group. Treatment with Lixelle® was conducted three times per week. Both the S-15 and S-35 columns were used, depending upon the size of the subject.

Joint pain was assessed using a standard 10 cm VAS scale, which is widely used and has been validated for assessment of pain.⁴ Activities of daily living were assessed using a modified Health Assessment Questionnaire (mHAQ).³ Osteolucency was evaluated before and after 1 year of Lixelle® treatment on radiographs of the hip and wrist joints. The number and area of the bone cysts were assessed independently by trained physicians unaware of the subject background and treatment. In hip joints, bone cysts greater than 5 mm were counted while in wrist joints, bone cysts greater than 2 mm were counted. Cystic area was also evaluated.

⁶ Kuragano T., Inoue T., Yoh K., Shin J., Fujita Y., Yoshiya K., Kim J., Sakai R., Sekita K., Goto T., Fukagawa M., Nakanishi T. Effectiveness of β 2-microglobulin adsorption column in treating dialysis-related amyloidosis: A multicenter study. *Blood Purif.* 2011; 32:317-322.

Results

Although the average age, time on dialysis, and β 2m levels were similar between the groups, the baseline number of bone cysts and the cystic area were greater in the Lixelle® group than in the HD group.

The ADL score, VAS pain score, and nocturnal awakenings improved over the 12 months of the Lixelle® β 2m apheresis column treatment. VAS pain decreased from a mean of approximately 9 at the beginning of the Lixelle® treatment to a mean of approximately 5 at the end of the treatment. The ADL scores also improved at the end of twelve months.

In the Lixelle® group, decreases in the number of bone cysts in the wrist and hip were observed, while there were no changes in the HD alone group. Cystic area per bone cyst decreased from 12.0 ± 12 to 9.3 ± 12 mm² in the wrist joint. The change in cystic area declined for the hip joints as well, but the changes were not statistically significant according to the study authors. In the HD group, cystic area per bone cyst increased for both the hip and wrist joint.

Cystic area per subject in the Lixelle® group decreased or remained constant for the Lixelle® group; while it increased for both wrist and hip joints for the HD group.

The limitations of this study are that it enrolled a small number of subjects and assessed subjective outcomes (pain, nocturnal awakening, ADLs) without blinding the subjects or investigators. Compared to the other studies used to support probable benefit, this study did not include histologic confirmation for diagnosis of DRA. It is unclear whether the observed differences in bone cysts are clinically significant. Furthermore, the author noted that more accurate measurement of the changes in bone cysts by CT and other imaging modalities may be useful.

Summary

This study was a prospective trial of 39 subjects diagnosed as having DRA based on the presence of DRA symptoms and the radiographic evidence of bone cysts. A retrospective control group of 28 subjects was selected, who had undergone long term hemodialysis and also had radiographic evidence of bone cysts, but no clinical symptoms of DRA. The results show:

- Improvements in subjective measures, such as pain and ADL;
- Improvements in the number and size of bone cysts for the Lixelle® treated group with no improvements or changes seen in subjects treated with HD alone.

While the control group in this study may have represented a slightly different population, the Lixelle® treated group did have a reduction in cyst number and cyst size for several joints compared to baseline assessments. While there is no definite clinical significance for these changes, they are still worth considering in the determination of probable benefit.

Summary of Post-market Safety Data

The Lixelle® β 2m apheresis column has been approved for use in Japan since 1994 and has been marketed in Japan since 1996. A prospectively monitored post-market study was conducted between 1994 and 1997, with data collected on 183 patients (13,476 treatments) at 58 centers. A complete list of the adverse events collected in this study is provided in the Table below. The most common adverse events by percentage of patients were temporary hypotension and a decrease in hematocrit. These are common adverse events for dialysis patients or for any extracorporeal therapy. The Incidence Rate included in the Table below is on a per treatment basis.

	Incidence	Incidence Rate (%)	Patient Number	Patient (%)
Adverse clinical events				
Hypotension	156	1.16	26	14.2
Hypovolemia	105	0.779	6	3.3
Palpitation	40	0.297	3	1.6
Decrease of hematocrit	37	0.275	9	4.9
Increase of Pain	30	0.223	1	0.5
Fatigue / Malaise	11	0.082	3	1.6
Anemia	9	0.067	4	2.2
Vomiting / Nausea	5	0.037	5	2.7
Chill / Shiver	3	0.022	3	1.6
Hypertension after dialysis	2	0.015	1	0.5
Pharyngeal pain	2	0.015	1	0.5
Thrombocytopenia	2	0.015	2	1.1
Abdominal pain	1	0.0074	1	0.5
Chest discomfort	1	0.0074	1	0.5
Chest oppression	1	0.0074	1	0.5
Dyspnea	1	0.0074	1	0.5
Total	406	3.01	46	25.1
Adverse technical events				
Blood clotting in hemodialyzer	129	0.957	7	3.8
Blood clotting in column	127	0.942	8	4.4
Blood clotting in tubing	7	0.052	5	2.7
Total	263	1.95	20	10.9

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KANEKA CORPORATION

2-3-18, Nakanoshima Kita-ku,
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546 Fifth Avenue, 21st Floor
New York, New York 10036