

SUMMARY OF SAFETY AND PROBABLE BENEFIT (SSPB)

I. GENERAL INFORMATION

Device Generic Name: β 2-microglobulin Apheresis Column

Device Trade Name: Lixelle[®] β 2-microglobulin Apheresis Column

Device Procode: PDI

Applicant's Name and Address: Kaneka Pharma America LLC
546 Fifth Avenue, 21st Floor
New York, NY 10036

Date of Panel Recommendation: None

Humanitarian Device Exemption (HDE) Number: H130001

Humanitarian Use Device (HUD) Designation Number: H08-0208

Date of HUD Designation: July 24, 2009

Date of Notice of Approval to Applicant: March 5, 2015

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).

The indication for use statement has been modified from that granted for the HUD designation. The HUD designation was for "use in the treatment of clinically diagnosed dialysis-related amyloidosis (DRA)." It was modified for the HDE approval for clarity.

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.

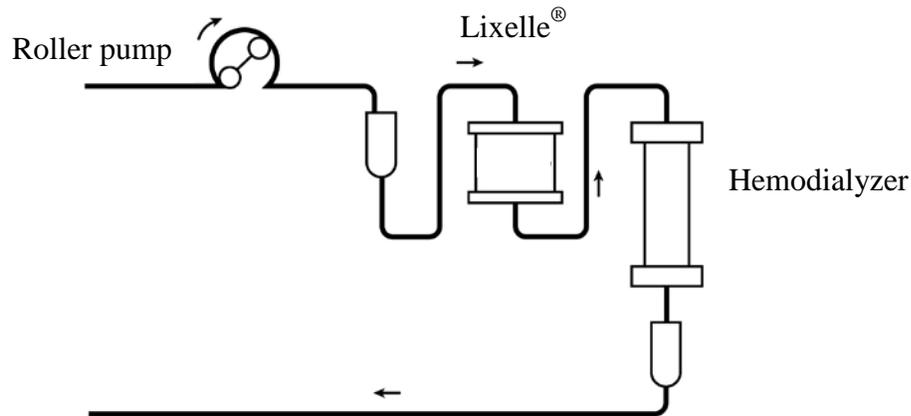
IV. WARNINGS AND PRECAUTIONS

The warnings and precautions may be found in the Lixelle[®] β 2-microglobulin Apheresis Column labeling.

V. DEVICE DESCRIPTION

The Lixelle[®] β 2-microglobulin apheresis column is a sterile 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.

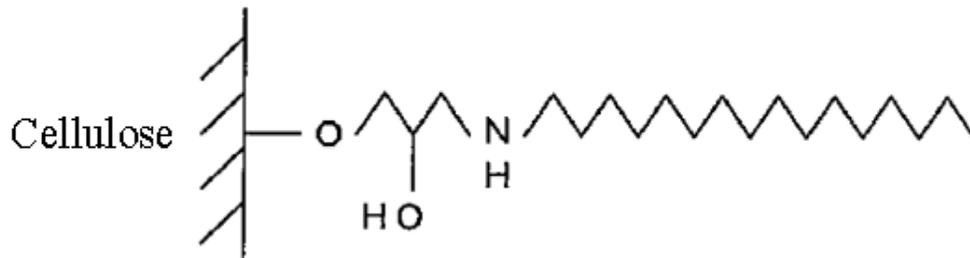
Figure 1: Lixelle[®] column in Hemodialysis blood circuit



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 combination of hydrophobic interaction and pore size of the 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.¹

It has been shown that the Lixelle[®] column 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 (3) models (see Table 1): 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).

Table 1: Model numbers, column capacity and extracorporeal volume

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

Figure 3 is a schematic diagram of the Lixelle® column. Table 2 lists the materials of each component. The column body (item 2) and inlet/outlet ends (item 4) provide the structure for the column. The ends of the column have standard Luer lock connectors that are plugged with sealing stoppers (item 7). The side of the column body has a cap (item 5) covered with a stopper (item 6). During manufacturing, the adsorbent and column solution (item 1) are added to the column via the cap, and then the stopper is placed over the cap. The adsorbent has a mean granule diameter of 460 µm. The mesh ring (item 3) has a mesh size of 120-180 µm, preventing the passage of the adsorbent out of the column, while allowing the flow of the filtered blood.

Figure 3: Diagram of Lixelle® Apheresis Column

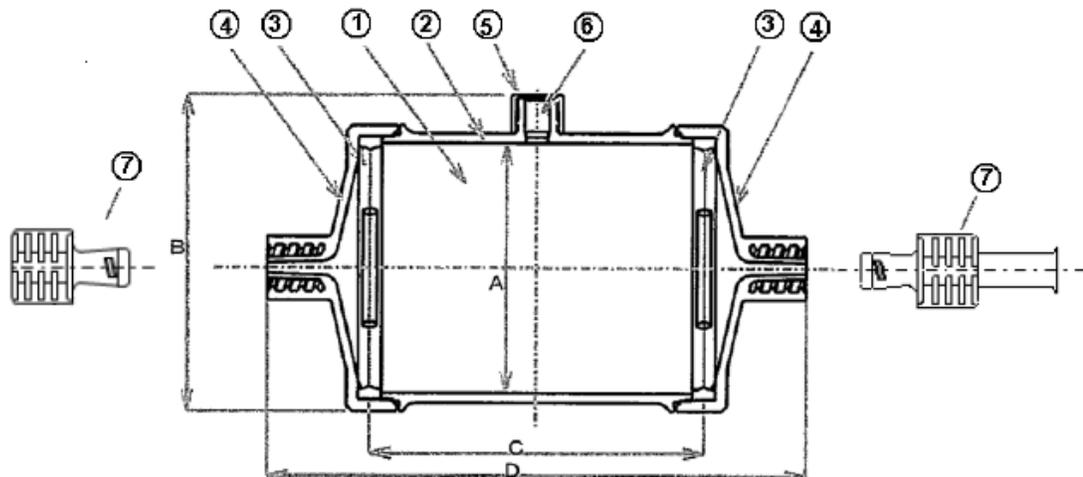


Table 2: Materials used in Lixelle[®] Column

Number (Figure 3)	Component	Material	Blood-contact?
1	Adsorbent and column solution	hexadecylamine-fixed cellulose beads in mixture of citric acid solution and sodium citrate solution	Yes
2	Column body	Polypropylene (CAS No. 9003-07-0)	Yes
3	Mesh ring	Styrene elastomer Mesh: Polyethylene terephthalate	Yes
4	Inlet/Outlet ends	Polypropylene (CAS No. 9003-07-0)	Yes
5	Cap	Polycarbonate	No
6	Stopper	Silicone rubber	Yes
7	Sealing stopper	Silicone rubber, polypropylene, styrene elastomer and phthalocyanine blue	No

The column is sterilized by moist heat at 121-124°C and packaged in a heat-sealed plastic bag.

The quality system of the manufacturing facility conforms to ISO 13485:2003. Final washing, assembly, sterilization, and packaging are performed in an ISO 14644-1 Class 8 clean room. Sterilization and packaging for the device conform with the following standards:

- ISO 17665-1:2006 - Sterilization of health care products -- Moist heat -- Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices
- ISO 11607-1:2006 - Packaging for terminally sterilized medical devices -- Part 1: Requirements for materials, sterile barrier systems and packaging systems
- ISO 11607-2:2006 - Packaging for terminally sterilized medical devices -- Part 2: Validation requirements for forming, sealing and assembly processes

Principle and Method of Operation

The Lixelle[®] β2m Apheresis column is attached to the arterial line of a dialysis circuit and to a connecting tube that is compatible with hemodialysis; the combination is rinsed and primed. The hemodialyzer is attached downstream from the column using the connecting tube and then connected to the venous line of the dialysis circuit. The Lixelle[®] column, tubing set, and hemodialyzer are rinsed and primed with heparinized physiological saline solution. After being primed, the circuit is connected to the patient, and the patient's blood is withdrawn by a blood pump. The blood passes through the column, β2m is adsorbed selectively, and the filtered blood passes through the hemodialyzer and is returned to the patient. Duration of a given procedure is linked to the length of the time needed for dialysis to obtain an adequate Kt/V. The frequency of the treatment is generally expected to be three (3) times per week.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Currently there is no device indicated for treatment of DRA in the U.S. Treatment strategies include symptom palliation or methods to enhance removal of β 2m from the blood. Palliative options include surgical removal of amyloid deposits and the use of anti-inflammatory drugs to mitigate pain and inflammation. Kidney transplantation, which improves kidney function and β 2m removal, is the preferred treatment for DRA, as it typically improves symptoms and may prevent progression of the disease. However, patients may not have the option for kidney transplantation as a potential treatment because of organ availability or other eligibility issues. High flux hemodialysis membranes, which are used in the majority of U.S. hemodialysis patients, are more effective at removing β 2m than lower flux membranes; however, patients may develop DRA despite the use of high flux membranes. Hemodiafiltration and extended hemodialysis therapies (i.e., nocturnal hemodialysis) are valid options for enhanced removal of β 2m, but are not widely available in the U.S.

VII. MARKETING HISTORY

The Lixelle[®] β 2m Apheresis Column has been marketed only in Japan, starting in 1996. The device was approved for marketing in Europe by TÜV SÜD as a Class IIb device, but the company has chosen not to market the device in Europe at this time. More than 4,200,000 units have been sold in Japan since approval.

The Lixelle[®] β 2m Apheresis Column has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device:

International Marketing Experience

- Hypotension
- Anemia / decreased hematocrit
- Hypovolemia
- Nausea / Vomiting
- Fatigue/malaise
- Palpitations
- Chills/shivering
- Thrombocytopenia
- Chest pain
- Dyspnea
- Increase of pain
- Hypertension after dialysis
- Abdominal pain
- Pharyngeal pain

- Clotting of the extracorporeal circuit and blood loss

Published Scientific Literature for Other Extracorporeal Therapies

- Cardiac dysrhythmia
- Muscle cramping
- Itching
- Headache
- Dizziness/fainting
- Hemolysis
- Hematoma formation at the venipuncture site
- Removal of other useful substances from the blood
- Anaphylaxis or allergic / hypersensitivity reaction
- Infection / microbial contamination

Many of the risks listed above are not that different from the risk of hemodialysis and extracorporeal therapies in general. However, the device does require the addition of an extra column to the existing extracorporeal circuit, so the overall risk is expected to be greater than with hemodialysis alone. The increased extracorporeal fluid volume can 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 because patients are exposed to additional biomaterials. The addition of the Lixelle[®] column also increases the potential for removal of beneficial substances from the blood.

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

The preclinical studies include biocompatibility, bench testing, animal testing, and shelf life testing. These are described in more detail below.

A. Biocompatibility

Objective: The objective of the biocompatibility studies was to demonstrate that the Lixelle[®] column materials are biocompatible for the intended use.

The Lixelle[®] column contains porous, spherical cellulose beads with covalently linked hexadecyl groups as ligands. When evaluated in accordance with the FDA Blue Book Memorandum #G95-1, entitled Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing.", the device is considered a prolonged circulating-blood-contacting, externally-communicating device. The two (2) main components of the device are the beads and column casing; the column casing includes four (4) materials. The beads were tested separately from the column casing and the same set of tests was performed for each component (beads and column casing). As

shown in Table 3, the Lixelle[®] column materials passed all required tests, demonstrating that the materials are safe and biocompatible for the proposed use.

Table 3: Summary of biocompatibility tests for Lixelle[®] column materials

Test	Test Method	Test Article	Results
Cytotoxicity	ISO Elution Method	Beads	Not cytotoxic
		Column Casing	Not cytotoxic
Sensitization	ISO Guinea Pig Maximization (0.9% SC Extract and SO Extract)	Beads	Not a sensitizer
		Column Casing	Not a sensitizer
Irritation	ISO Intracutaneous Study in Rabbits (0.9% SC Extract and SO Extract)	Beads	No irritation. Beads met requirements of test.
		Column Casing	No irritation. Column materials met the requirements of the test.
Acute Systemic Toxicity	ISO Systemic Toxicity Study in Mice (0.9% SC Extract and SO Extract)	Beads	No evidence of systemic toxicity. Beads met requirements of the test
		Column Casing	No evidence of systemic toxicity. Column materials met the requirements of the test.
Pyrogenicity	USP Material Mediated	Beads	Non-pyrogenic
		Column Casing	Non-pyrogenic.
Subchronic Toxicity	Two Week Systemic Toxicity in the Rat, Repeated Parenteral Administration of two extracts	Beads	No evidence of systemic toxicity.
		Column Casing	No evidence of systemic toxicity
Genotoxicity	Bacterial Reverse Mutation Study (0.9% SC Extract and DMSO Extract)	Beads	Non-mutagenic
		Column Casing	Non-mutagenic
Genotoxicity	Mouse Lymphoma Assay (RPMI Serum free extract and DMSO Extract)	Beads	Not mutagenic
		Column Casing	Not mutagenic
Genotoxicity	Mouse Peripheral Blood Micronucleus Study (0.9% SC Extract and SO Extract)	Beads	Did not introduce micronuclei in mice.
		Column Casing	Did not introduce micronuclei in mice

Test	Test Method	Test Article	Results
Implantation	ISO Muscle implantation study in Rabbits: 2 weeks	Beads	The macroscopic reaction was not significant compared to the negative control. Microscopically, test article was classified as slight irritant compared to the negative control article.
		Mesh, Mesh Ring	The macroscopic reaction was not significant. The mesh was classified as a non-irritant compared to the negative control article, while the mesh ring was a slight irritant compared to the negative control article.
		Column Body and Cylindrical stopper	Macroscopic reaction was not significant compared to negative control. Microscopically, each test article was a non-irritant.
Implantation	ISO Muscle implantation study in Rabbits: 6 weeks	Beads	Macroscopic reaction was not significant compared to negative control. Microscopically, the test article was classified as a slight irritant compared to the negative control article.
		Mesh, Mesh ring	The macroscopic reaction for each test article was not significant as compared to the negative control. Microscopically, the mesh was a slight irritant, and the mesh ring was a non-irritant compared to the negative control.
		Column body, cylindrical stopper	The macroscopic reaction for each test article was not significant compared to the negative control article. Microscopically, each test article was a non-irritant compared to the negative control.
Hemocompatibility	ASTM Hemolysis Study	Beads	Non-hemolytic
		Column	Non-hemolytic
Hemocompatibility	SC5b-9 and C3a Complement Activation	Beads	Not a potential activator of complement in SC5b-9 assay. The C3a assay was statistically lower than negative control, suggesting that non-specific binding was occurring.
		Column	Not a potential activator of complement in SC5b-9 or C3a assay.

B. Performance Testing

Objectives: The objectives of the performance testing studies were to evaluate the Lixelle[®] column for β 2m adsorption, selectivity, passage of blood components, complement activation, microparticle leakage, and differential pressure. Tests were performed both at the recommended flow rate (250 ml/min) and at a higher flow rate (500 ml/min). All of these properties were evaluated in bench testing; passage of blood

components was also evaluated in animal studies; complement activation was also evaluated in human studies.

Testing was performed either with a “Mini-column” or with a standard Lixelle[®] column. The mini-column contained the same Lixelle[®] beads and used the same linear velocity as the Lixelle[®] column. Either human blood or bovine blood was used for the tests, with the exception of the microparticle leakage test which utilized saline.

In vitro β2m adsorption study

β2m was dissolved in commercial human serum with initial concentration of 16, 32, 62, and 93 mg/L. The β2m-containing serum was mixed with Lixelle[®] adsorbent in ratio of 14.4 ml serum/0.4 ml adsorbent, agitated, and incubated for 4 h at 37°C. The separated supernatant was measured for β2m concentration by radioimmunoassay.

The study showed that the amount of the β2m adsorbed linearly in proportion within the initial β2m concentration in range of 16 – 93 mg/L with 73-78% β2m were removed from the serum. Results are presented in Table 4, below.

Table 4: In vitro β2 –microglobulin adsorption

Sample Number		1	2	3	4
β2M concentration (mg/L)	Initial (Cb)	16	32	62	93
	After 4 hours (Ca)	3.5	7.0	15	25
β2M adsorbed (mg/ml of adsorbent)		0.45	0.90	1.7	2.4

In vitro Selectivity Testing

Selectivity for β2m was determined based on lack of adsorption of various other blood components. Blood taken from healthy humans was allowed to stand at 37°C for one (1) hour and then centrifuged at 3,000 rpm for 30 minutes at room temperature to obtain serum. Then 6 ml of the serum 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 serum was mixed with 0.5 ml of isotonic saline instead of adsorbent. The results presented in Table 5, below, demonstrates the selectivity of the Lixelle[®] column and shows that the Lixelle[®] column has little effect on total protein, albumin, immunoglobulins, and other important blood components.

Table 5: In vitro adsorption of blood components by Lixelle® beads

Component	Serum 1		Serum 2		Serum 3	
	Before	After	Before	After	Before	After
Total protein (mg/dl)	7.2	7.1	6.7	6.7	7.4	7.4
Albumin (mg/dl)	4.4	4.3	4.0	4.1	4.1	4.1
IgG (mg/dl)	1241	1254	1165	1128	1622	1650
IgA (mg/dl)	299	306	208	205	303	299
IgM (mg/dl)	78	86	257	244	253	272
C3 (mg/dl)	76.9	78.2	84.2	83.7	68.5	72.7
C4 (mg/dl)	18.8	19.8	33.0	33.9	33.4	36.0
C5 (mg/dl)	7.6	7.2	8.3	8.3	9.8	9.4
Total cholesterol (mg/dl)	213	213	212	215	164	165
Triglycerides (mg/dl)	166	161	218	215	71	70
GOT (U/l)	32	32	15	16	13	13
GPT (U/l)	48	49	22	22	8	9
ALP (U/l)	191	187	267	267	113	111
LDH (U/l)	373	371	350	352	289	294
CPK (U/l)	126	124	184	188	55	55
Glucose (mg/dl)	79	73	83	76	79	74
Cortisol (µg/dl)	17	14	8.4	7.1	14	12
T3 (µg/ml)	1.3	1.1	1.4	1.0	1.2	1.0
T4 (µg/dl)	7.6	7.6	6.4	6.0	7.6	8.3
Total bilirubin (mg/dl)	0.7	0.7	0.6	0.6	0.4	0.4
Creatinine (mg/dl)	1.0	1.0	1.1	0.9	0.9	0.8
Uric acid (mg/dl)	7.1	5.7	4.9	3.9	4.2	3.5

In similar testing, the Lixelle® column was found to adsorb other blood components. Table 6, below, shows components having adsorption rates of 20% or more; in some cases the serum was from healthy humans, in other cases serum from dialysis patients was used given that many of these substances are present at higher levels in these patients. Gastrin, ACTH, insulin, osteocalcin, PTH-intact, lysozyme, myoglobin and retinol binding protein were removed at high rates by the column; these higher adsorption rates are noted in the product labeling as potential side effects of the device. In addition to bench studies, two (2) clinical studies (Gejyo *et al*, 1994² and Nakazawa *et al*, 1993³) evaluated removal of substances from the blood with the Lixelle® column *in vivo*. These studies largely supported the findings of the *in vitro* studies. Other minor changes were noted in some of the serum biochemical parameters assessed, but these were not considered to be clinically meaningful.

Given that these biochemical changes were not assessed in a long-term study, FDA requested that the sponsor add the following statements to the labeling:

The addition of the Lixelle[®] column to the extracorporeal circuit also increases the potential for removal of beneficial substances from the blood.

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.

Table 6: 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 adsorbent. Data are 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.

Additional bench testing showed that perfusion at higher flow rates (500 ml/min) or for longer time periods (i.e., 6 hours) did not affect the selectivity of the Lixelle® beads.

The potential adsorption of electrolytes was also evaluated as shown in

Table 7. The results show that Lixelle® has little if any effect on electrolyte levels in blood.

Table 7: In vitro adsorption of electrolytes by Lixelle® beads

Electrolyte	Concentration					
	Serum 1		Serum 2		Serum 3	
	Before	After	Before	After	Before	After
Sodium (mEq/l)	144	142	145	140	141	143
Potassium (mEq/l)	3.5	3.3	3.4	3.1	3.2	3.0
Calcium (mg/dl)	9.1	8.6	8.8	8.4	8.8	8.4
Magnesium (mg/dl)	2.1	2.0	1.8	1.7	2.1	1.9
Chlorine (mEq/l)	106	106	107	106	108	109
Iron (µg/dl)	95	94	121	123	46	47

Passage of Blood Components

Blood was collected from four (4) healthy volunteers and heparinized with 7 IU/ml. The heparinized blood was passed through a mini-column using flow rates that simulate clinical use.

The adsorbent used in the column showed acceptable passability of all three (3) cellular components of blood (red blood cells, white blood cells, and platelets). The change in percentage for each blood component, between the value observed when passing blood through a circuit alone, versus using a Lixelle® column was assessed, as reported in Table 8. Additional bench testing showed that perfusion at higher flow rates (500 ml/min) or for longer time periods (i.e., 6 hours) did not affect the selectivity of the Lixelle® beads.

Table 8: In vitro percentage of blood components passed through Lixelle® column

Blood Component	Component Passage (% , mean ± SD, n = 4)		
	10 minutes	20 minutes	30 minutes
Red blood cell	101.7 ± 2.8	99.1 ± 6.2	100.6 ± 1.7
White blood cell	84.8 ± 7.4	85.2 ± 1.3	85.8 ± 2.5
Platelet	72.9 ± 20.6	86.7 ± 22.8	103.1 ± 14.8

Passage of blood components was also evaluated *in vivo* in an animal model. Four (4) mix breed dogs weighing about 10 kg were anesthetized with Nembutal. A 50-mL adsorption column (31 mm inside diameter × 70 mm length) was attached to each dog and 2000 IU of heparin was injected intravenously to heparinize the dogs. Extracorporeal circulation was performed at 50 ml/minute for 3 hours for a total of 15 cycles. Blood was collected from a vein before and after the adsorption column at 15, 30, 60, 120, and 180 minutes after the start of extracorporeal circulation and examined hematologically.

The passage rate and change rate of blood cells at each measurement time are shown in Table 9. The percent passage of red blood cells varied only very slightly from 100% (individual data ranged from 98% to 103% over time), indicating that red blood cells were not captured by the adsorbent. Of note, values could exceed 100% in this study as the percentage reflects the proportion of the blood component relative to baseline (pre-column sample). Any “increase” from baseline is likely attributed to variability in the lab assay for the blood component. The change rates of white blood cells and platelets were calculated by adjusting counts with hematocrit values, since a decreased hematocrit would be due in whole or part to the extra volume of replacement fluid. The percentage passage of white blood cells and platelets were low for the first 60 minutes, but climbed to over 90% at 120 minutes and beyond.

Table 9: Blood Component Passage for Lixelle® column in canine model.

Blood Component	Component Passage (%; mean ± SD; n = 4):				
	15 minutes	30 minutes	60 minutes	120 minutes	180 minutes
Red blood cell	100.1 ± 1.0	99.9 ± 1.3	99.9 ± 1.3	99.5 ± 1.4	99.9 ± 1.0
White blood cell	37.8 ± 31.5	20.0 ± 11.8	53.7 ± 38.4	97.8 ± 21.1	104.3 ± 11.2
Platelet	12.8 ± 26.7	6.6 ± 15.0	49.2 ± 54.5	94.6 ± 20.2	101.3 ± 5.9

The contents of samples taken from a vein before the adsorption column at each time point were compared to baseline values to assess the *in vivo* change of blood content due to use of the Lixelle column. These results are presented in Table 10 below and show that the red blood cell, white blood cell, and platelet counts all stayed at or above 70% of their baseline values.

Table 10: In vivo change (compared to baseline) in blood components in canine model

Blood Component	Component Change (%; mean ± SD; n = 4)				
	15 minutes	30 minutes	60 minutes	120 minutes	180 minutes
Red blood cell	94.8 ± 3.5	91.7 ± 5.0	92.6 ± 6.7	92.3 ± 6.1	89.5 ± 7.9
White blood cell	91.3 ± 16.5	85.7 ± 18.2	80.2 ± 22.0	70.0 ± 21.0	75.8 ± 31.9
Platelet	100.3 ± 5.2	93.9 ± 9.4	89.5 ± 10.3	82.5 ± 24.5	82.4 ± 29.4

Complement Activation

The potential for complement activation was evaluated in both *in vitro* and *in vivo* testing. Some complement activation was observed in these bench tests. However, there was no worsening of hemolysis and no coagulation (as shown by fibrinogen levels).

In the *in vivo* tests, data were collected on five (5) patients as part of a clinical study. A Lixelle[®] column and a dialyzer were connected in series. Blood was collected from the inlet and outlet of the device at 0, 30, 60, and 120 minutes after the initiation of treatment and at the end of the procedure. Complement C3a, C4a, and C5a were measured. The procedure was repeated during 2 to 5 clinic sessions, depending on the patient. Passage through the adsorber resulted in a mild increase in C3a. C4a decreased after the start of the extracorporeal circulation. C5a showed a negligible change over time. Based on these results, it was concluded that the Lixelle[®] column had negligible effect on complement activation.

Microparticle Leakage Test

To evaluate microparticle leakage, the device was first vibrated according to standards and then connected to the appropriate blood tubing and rinsed. Filtered water was then perfused through the column at a flow rate of 200 ml/min for 4 hours using a blood pump. Effluent was collected at 0, 1, 2, 3 and 4 hours, and the numbers of particles that were 5 µm or more in size were counted using an automated micro particle counter.

The results showed that the device met specification (particles ≥ 5 µm should be less than 10/ml), even when higher flow rates were used.

Differential Pressure Test

Safety at a blood flow rate of 500 ml/min was assessed with an *in vitro* study, in which heparin anti-coagulated bovine blood was perfused through a Lixelle S-15 column at 500 ml/min for 4 hours. The differential pressure between the inlet and outlet of the column was measured every 5 minutes for the first 30 minutes and every 30 minutes thereafter; counts of erythrocytes, leukocytes, and platelet counts between the inlet and outlet of the column were measured; and hemolysis was also evaluated by measuring absorbance of plasma at 570nm every 15 minutes up to 90 minutes and every 30 minutes thereafter until 4 hours.

The study found that no liquid layer was generated within the column during the perfusion and no sudden increase of differential pressure was noted as a result of deformation of the adsorbent. Penetration of erythrocytes, leukocytes and platelets through the column showed that cell counts measured at the initiation of perfusion were maintained at 100%, 99% and 94%, respectively, after 4 hours of perfusion. Hemolysis was not observed. Based on the results of this testing, a flow rate of 500 mL/min does not appear to introduce any significant safety concerns.

C. Shelf Life Testing

The shelf life of the Lixelle[®] column is 2 years. This shelf life is supported by real-time stability studies which evaluated residuals, endotoxin, immobilized and eluted ligand,

eluted substances, microparticle leakage, and biological safety. In addition, pressure testing and sterility testing were conducted to demonstrate that device integrity and sterility are maintained at 2 years.

X. SUMMARY OF CLINICAL INFORMATION

The Lixelle[®] column has been studied in numerous small clinical trials with results published in the literature. The four (4) key studies that were evaluated to assess the safety and probable benefit of the Lixelle[®] column are described in the section below.

Study by Geivo, et al. (2004)⁴

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 Lixelle[®] (S-35) β 2m apheresis column (Lixelle[®] group). Long-term dialysis patients were enrolled who had one of the following: (a) 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 3 months for shoulders, elbows, joints of the hands, hip joints, knees, legs, feet, and joints of the neck, according to a four (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 (2) physicians who were blinded to the subjects' background and treatment.

Results

Data supporting 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 (Activities of Daily Living (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 (2) 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 one (1) subject (4.5%) developed pharyngeal pain. Lixelle[®] treatment was discontinued for six (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 (2) 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 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 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)⁵

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; and (4) bone cysts detected by radiographic imaging.

Five (5) subjects dropped out of the study. Four (4) subjects voluntarily withdrew and one (1) subject was transferred to another hospital for surgery. During Year 1, subjects were treated for 4 hours three (3) 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,⁶ and joint pain, which was assessed using a validated 10cm Visual Analog Scale (VAS) that has been widely used in pain studies.⁷ 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 (1) 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.

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 (2) 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)⁸

This was a 2-year study that enrolled 20 subjects. Patients were included if they had chronic renal failure and DRA based on the following inclusion criteria: (1) proven presence of tissue deposition of amyloid with β 2m confirmed by surgery or biopsy; (2) dialysis treatment for at least 10 years and had undergone carpal tunnel surgery; (3) bone cysts detected by radiographic imaging.

Treatment with Lixelle[®] was conducted three (3) 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 10cm VAS scale, which is widely used and has been validated for assessment of pain.⁷ Activities of daily living scores were assessed using a modified Health Assessment Questionnaire (mHAQ).⁶ 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 (6) months.

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

Results

Three (3) of the 20 enrolled subjects dropped out of the study. One (1) subject died three (3) months after the start of the study with severe cardiovascular disease and two (2) 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 12 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.

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 hemodialysis alone followed by Year 2 of hemodialysis 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)⁹

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 (3) 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 10cm VAS scale, which is widely used and has been validated for assessment of pain.⁷ Activities of daily living were assessed using a modified Health Assessment Questionnaire (mHAQ).⁶ 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.

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 (12) 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® β2m 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

Table 11. 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 Table 11 below is on a per-treatment basis.

Table 11: Adverse Events observed in Post-market study of Lixelle® column conducted in Japan

	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

XI. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The referenced clinical studies included 132 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data. For the published studies relied upon in this HDE application, no single published study made a significant contribution to the demonstration of safety or probable benefit. Of note, Kaneka did sponsor the post-market study in Japan (described above), which included an additional 60 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the post-market data.

XII. RISK PROBABLE BENEFIT ANALYSIS

Summary of the Benefits

In dialysis related amyloidosis (DRA), there is an accumulation of beta-2 microglobulin (β_2m), leading to clinical manifestations including carpal tunnel syndrome, bone cysts, pathologic fractures, and swollen painful joints. The Lixelle[®] β_2m apheresis column has been shown to decrease levels of β_2m in bench and clinical studies.

Four (4) key studies provide supporting evidence of the probable benefit of β_2m removal. The studies include both objective (improvement in grip/pinch strength, decrease in bone cyst formation and size) and subjective (reduction in joint pain/stiffness, improved activities of daily living) measures of clinical improvement.

The key studies show improvement in these measures either as compared to a control group receiving hemodialysis without Lixelle[®] or to the subjects' own baseline values. The probable benefit appears to be maintained during the course of treatment with the device (12-24 months in the clinical studies).

Summary of the Risks

In the Japanese post-market study of 183 patients, hypotension was noted in 14.2% of subjects and occurred at a rate of 1.16% per treatment. Anemia (also defined as decreased hematocrit) was noted in 2-5% of subjects and occurred at a rate of up to 0.28% per treatment. The next most frequent (% of subjects) clinical AEs included, hypovolemia (3.3%), nausea/ vomiting (2.7%), fatigue/malaise (1.6%), heart palpitations (1.6%), chills/shivering (1.6%), and thrombocytopenia (1.1%), all of which occurred at frequencies of <1% per treatment. Technical AEs, which included blood clotting in the column, dialyzer, and tubing were noted in 2.7-4.4% of subjects, and, when considered together, occurred in about 2% of treatments.

Among the four (4) smaller clinical studies described above, the rate of clinical adverse events (AE) varied. The most common reported AEs were hypotension and anemia, which occurred in up to 27% and 18% of subjects, respectively, in the study by Gejyo, et al. (2004). There were no reported serious AEs, but they were not systematically assessed. The AEs were generally transient and occurred around the time of treatment. There were no safety data available for controls, but these types of events are not uncommon with extracorporeal therapy in general.

However, the device does require the addition of an extra column to the existing extracorporeal circuit, so the overall risk is greater than with dialysis alone. The increased extracorporeal fluid volume can lead to a greater risk of hypotension, clotting, and blood loss. There are additional tubing connections, which increase handling and the risk of contamination and infection. There is also the risk of allergic reactions, because patients are exposed to additional biomaterials. Other risks may include the removal of additional substances from the blood with the column.

Summary of Other Factors

There is a fair amount of uncertainty with the results of the referenced studies, primarily due to study design issues which could introduce bias into the results. For the benefit outcomes, Lixelle[®] treatment resulted in improvements in several objective measures, but it is not clear if these increases were clinically significant. For the subjective benefit outcomes, most of the studies used validated assessment tools (pain, ADL, etc.). However, the lack of blinding of subjects and investigators to the treatment limits the conclusions which can be drawn from these data.

The reported safety outcomes from the four (4) key studies were only descriptive and did not appear to be systematically assessed. However, safety data was the main focus of the Japanese post-market study which helped to reduce the level of uncertainty with regards to safety of the device. There is some uncertainty in terms of whether the data obtained from outside the United States (OUS) can be generalized to the US population, but the types of risks appeared to be consistent across studies. Of note, the Japanese clinical studies used lower blood flow rates (150-250ml/min) during hemodialysis treatments than are typically used in the U.S. However, Kaneka Pharma America LLC has agreed to label the device with a maximal blood flow rate of 250ml/min.

The Lixelle[®] S-25 (250 ml capacity, 105 ml extracorporeal volume) column was not used in any of the referenced key clinical studies, but has been marketed in Japan with the other Lixelle[®] columns. However, FDA believes that the benefits and risks of this “medium” sized column should be similar to and “bracketed” by the S-35 (350 ml capacity, 177 ml extracorporeal volume) and S-15 (150 ml capacity, 65 ml extracorporeal volume) columns, which were used in the studies.

DRA is a chronic progressive condition that generally gets worse over time due to the continued accumulation of β_2m . There are some alternative therapies, but they may not be available to every dialysis patient in the U.S. This device may address an unmet need for these patients who may not be eligible for renal transplantation or may not have access to novel therapies such as extended dialysis or hemodiafiltration.

There are no data to suggest how much risk DRA patients are willing to tolerate for a given degree of benefit. However, given the severity of symptoms and lack of alternative therapies, it is likely that patients would accept a therapeutic trial of this therapy, especially given a risk profile that is similar to hemodialysis.

Conclusions

In summary, the totality of the evidence from the key studies, the post-market safety study, and the additional supportive literature studies provide support for a determination that the device does not pose an unreasonable risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment and considering the proposed indication for use for the device.

FDA believes any remaining uncertainty regarding risks can be addressed with the proposed post-market study of the device in the U.S. population and/or mitigated through detailed device labeling.

XIII. PANEL RECOMMENDATION

The HDE was not taken to a meeting of the Gastroenterology-Urology Panel because it was determined that the nonclinical and clinical issues raised by the HDE did not require panel review.

XIV. CDRH DECISION

CDRH has determined that, based on the data submitted in the HDE, the Lixelle[®] β 2-microglobulin Apheresis Column will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from using the device outweighs the risks of illness or injury. CDRH issued an approval order on March 5, 2015. The final conditions of approval cited in the approval order are described below.

New Enrollment PAS for the Lixelle β 2m Apheresis Column: The applicant has agreed to conduct a study as follows: The purpose of the study is to evaluate the long-term safety and probable benefit of the Lixelle β 2m Apheresis Column for the treatment of patients with clinically-diagnosed dialysis related amyloidosis (DRA). This will be a prospective, multicenter, double arm study with a total of 40 newly enrolled patients treated at 3 to 15 clinical centers in the United States. The study participants will be followed for 24 months. The study population will consist of 30 DRA patients who will be treated with the device (treatment arm) and 10 patients who will be treated with conventional hemodialysis (HD) (natural history arm). All patients must agree to follow-up requirements, including questionnaires.

The primary study endpoint is the rate of every serious adverse event through two years of Lixelle treatment, compared by descriptive statistics to the rate in the natural history arm. Data on all adverse events will be collected. There are two secondary endpoints to assess the probable benefit of Lixelle in serum β 2m reduction rate

following a single Lixelle-treatment: (1) β 2m reduction rates obtained in any week from the 2nd to 7th week of follow-up, statistically compared with what was obtained the week of treatment with conventional HD; (2) β 2m reduction rates obtained in any week from the 46th to 53rd week of follow-up, statistically compared with what was obtained the week of treatment with conventional HD. Paired t-test will be used to compare the reduction rates at baseline with the observed rates at follow-up assessments.

There are four exploratory endpoints to assess the change in quality of life (QoL) evaluated by Dialysis-Related Amyloidosis Questionnaire (DRAQ) and Kidney Disease Quality of Life- Short Form (KDQoL-SF), pre-treatment serum β 2m, and bone cyst through two years of Lixelle-treatment.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality Systems (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATION

Directions for use: see device labeling.

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

Post-approval Requirements and Restrictions: see approval order.

XVI. REFERENCES

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