

SUMMARY OF SAFETY AND PROBABLE BENEFIT (SSPB)

I. GENERAL INFORMATION

Device Generic Name: LDL Apheresis System

Device Trade Name: Liposorber[®] LA-15 System

Device Procode: PBN

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

Humanitarian Device Exemption (HDE) Number: H120005

Humanitarian Use Device (HUD) Designation Number: H09-0211

Date of Humanitarian Use Device (HUD) Designation: January 28, 2010

Date(s) of Panel Recommendation: N/A

Date of Notice of Approval to Applicant: October 10, 2013

The original PMA (P910018) was approved on February 21, 1996 and is indicated for use in performing low density lipoprotein cholesterol (LDL-C) apheresis to acutely remove LDL-C from the plasma of the following high risk patient populations for whom diet has been ineffective or not tolerated: Group A – functional hypercholesterolemic homozygotes with LDL-C > 500 mg/dl; Group B – functional hypercholesterolemic heterozygotes with LDL-C ≥ 300 mg/dl; and Group C – functional hypercholesterolemic heterozygotes with LDL-C ≥ 200 mg/dl and documented coronary heart disease. The Summary of Safety and Effectiveness (SSED) to support the indication is available on the CDRH website: http://www.accessdata.fda.gov/cdrh_docs/pdf/p910018.pdf. The current HDE was submitted to expand the indication for the Kaneka Liposorber LA-15 System to include pediatric patients with primary focal segmental glomerulosclerosis (FSGS) or for post-renal (kidney) transplantation in pediatric patients with recurring primary FSGS.

II. INDICATIONS FOR USE

The Liposorber[®] LA-15 System is indicated for use in the treatment of pediatric patients with nephrotic syndrome associated with primary focal segmental glomerulosclerosis, when

- Standard treatment options, including corticosteroid and/or calcineurin inhibitors treatments, are unsuccessful or not well tolerated and the patient has a GFR ≥ 60 ml/min/1.73m² or
- The patient is post renal transplantation.

III. CONTRAINDICATIONS

This device must not be used in:

- a. patients who have been treated with ACE-inhibitors within the past 24 hours;

Severe anaphylactoid reactions including shock have been observed in patients treated with the Liposorber[®] LA-15 under concomitant ACE-inhibitor medication. The risk of an anaphylactoid reaction may be minimized by withholding the administration of ACE inhibitors for approximately 24 hours before each LDL-apheresis procedure. The time period to withhold ACE inhibitors should be prolonged, if determined by the treating physician, considering each individual's renal function and the biological half-life of the ACE-inhibitor currently in use. If required, ACE-inhibitor administration may be resumed on the day of the apheresis treatment but only after the apheresis treatment is complete.

- b. patients for whom adequate anticoagulation cannot be achieved, such as those with severe hemophilia, severe hemorrhage diathesis, severe gastrointestinal ulcers, or who are receiving vitamin K antagonist medications after surgery;
- c. patients for whom extracorporeal circulation therapy with Liposorber[®] LA-15 cannot be tolerated such as those with severe cardiac insufficiency, acute myocardial infarction, severe cardiac arrhythmia, acute apoplexy, or severe uncontrollable hypertension or hypotension; and
- d. patients with hypersensitivity to dextran, heparin or ethylene oxide.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Liposorber[®] LA-15 System labeling.

V. DEVICE DESCRIPTION

The Kaneka Liposorber[®] LA-15 System is an integrated extracorporeal blood processing system that includes disposable components and a control/monitor unit.

The components of the device are identical in material and design to the device currently approved via PMA P910018 and its supplements. The Liposorber[®] LA-15 System consists of the Sulflux KP-05 Plasma Separator, Liposorber[®] LA-15 Adsorption Columns, NK-M3R Tubing Set, and MA-03 Machine.

The Sulflux KP-05 Plasma Separator (approved on 6/27/2007 – Supplement 11) separates the plasma from whole blood. This component is comprised of porous hollow fibers made of polyethylene coated with an ethylene vinyl alcohol copolymer enclosed in a polycarbonate housing.

The Liposorber[®] LA-15 Adsorption Columns (approved in original PMA 1996) (Figure 1) are disposable. They adsorb apolipoprotein B-containing lipoproteins from a patient's

plasma as it passes through the column. The casing of the column is polycarbonate. Each column (they are used in pairs for a treatment) contains a microporous hydrophilic gel (with particle size of 64 – 160 μm) composed of 150 ml dextran sulfate cellulose (DSC) beads soaked in 0.04-0.08% (w/v) sodium citrate/citric acid solution.

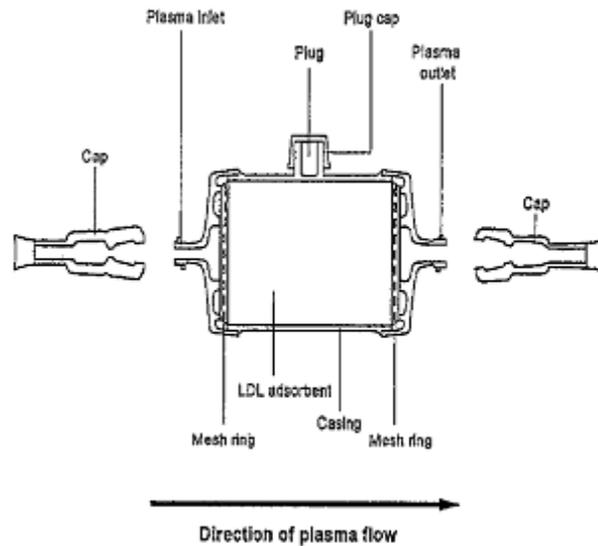


Figure 1. Schematic of Liposorber LA-15 Adsorption Column

The NK-M3R Tubing Set (approved on 3/31/2009 – Supplement 12 and 6/18/2010 – Supplement 13) set is designed specifically for the Liposorber[®] LA-15 System. The tubing is comprised primarily of polyvinyl chloride, but also contains polycarbonate, polypropylene, polyethersulfone, polytetrafluoroethylene, polyester, acrylic resin, isoprene rubber, and polyolefin elastomer. It is composed of the following:

- Blood withdrawal line
- Regeneration line
- Plasma line
- Blood return line
- A set of five (5) connection lines (for connection to solution bags)
- Membrane filter.

The MA-03 Machine (approved 3/31/2009 – Supplement 12) is a computer-controlled unit that controls the entire apheresis procedure.

While the Liposorber[®] LA-15 System (P910018) is labeled for either weekly or every other week use when used to treat familial hypercholesterolemia (FH) (depending on the patient's LDL-C levels), in this HDE, the Liposorber (H120005) is indicated for up to 12 uses in 3 months for treatment of FSGS (twice weekly for three (3) weeks, then weekly for six (6) weeks).

Principle and Method of Operation:

The method of operation for the device for its pediatric indication is identical to the method of operation for the original indication (P910018), which is to treat

hypercholesterolemia in certain high risk patient populations. The method of operation is described below and Figure 2 is the schematic of this operation.

- Blood is withdrawn from the patient's arm via venous access.
- The blood is combined with heparin and pumped at a steady flow rate through the NK-M3R Tubing Set into the inlet port of the Sulflux KP-05 Plasma Separator to separate plasma from the cellular components of the blood.
- Plasma exits from the plasma outlet and the remaining blood, including red and white blood cells and platelets, exit from the blood outlet.
- The cell-free plasma is pumped into one of the two Liposorber LA-15 Adsorption Columns where apolipoprotein B-containing lipoproteins are adsorbed to the cellulose beads and removed from the plasma. The dextran sulfate cellulose beads have a strong affinity for apolipoprotein B-containing lipoproteins.
- Filtered plasma exits the column, passes through a membrane filter to ensure particles from the column do not enter the system, and is recombined with the cellular elements originally exiting the plasma separator.
- This recombined blood and plasma flow through a built-in blood warmer (part of the MA-03 Machine) and is returned to the patient via a second venous access.

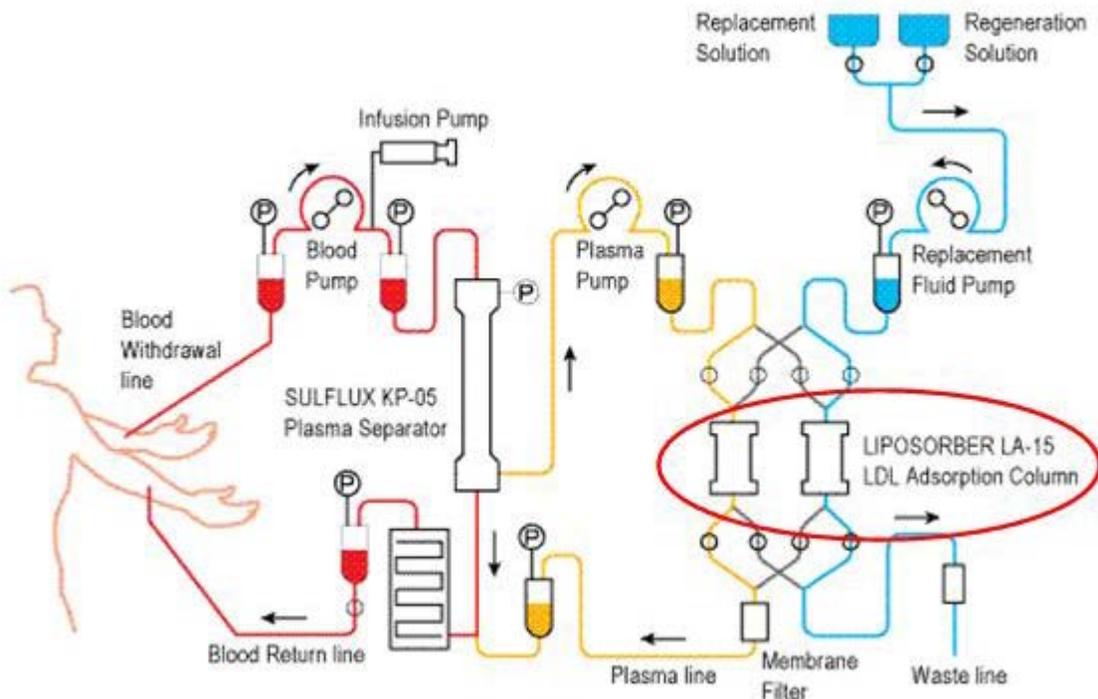


Figure 2. Schematic of Liposorber Operation

Apheresis occurs on a continual basis even when a column has been exhausted, because the system regenerates one column while the other one is in use. When one column has completed adsorbing, the computer-regulated machine automatically switches the plasma flow to the other column to continue adsorption. Simultaneously, the plasma remaining

in the first column is returned to the patient. The first column is then regenerated using 5% Sodium Chloride Injection USP. Once the elution is completed and flushed through the waste lines to a waste bag, the column is reprimed and ready for the next cycle of adsorption, allowing continuous apheresis. No additional fluids are given to the patient during these column switch overs and only the filtered plasma is returned. The process takes about 2-3 hours and is performed at a medical facility.

The total extracorporeal volume of the circuit (Figure 3) used with a Liposorber LA-15 Adsorption Column is 404 mL, which includes both plasma and whole blood together. The total volume of whole blood in the circuit is 160 mL. The total volume of additional plasma in the circuit is 244 mL. The entire system is primed with heparinized fluid before use, so the patient does not experience significant volume loss. The 244 mL plasma portion of the circuit is drawn from and returned to the blood portion of the circuit. Thus, the effective increase in the patient's blood volume is only 160 mL and not 404 mL.

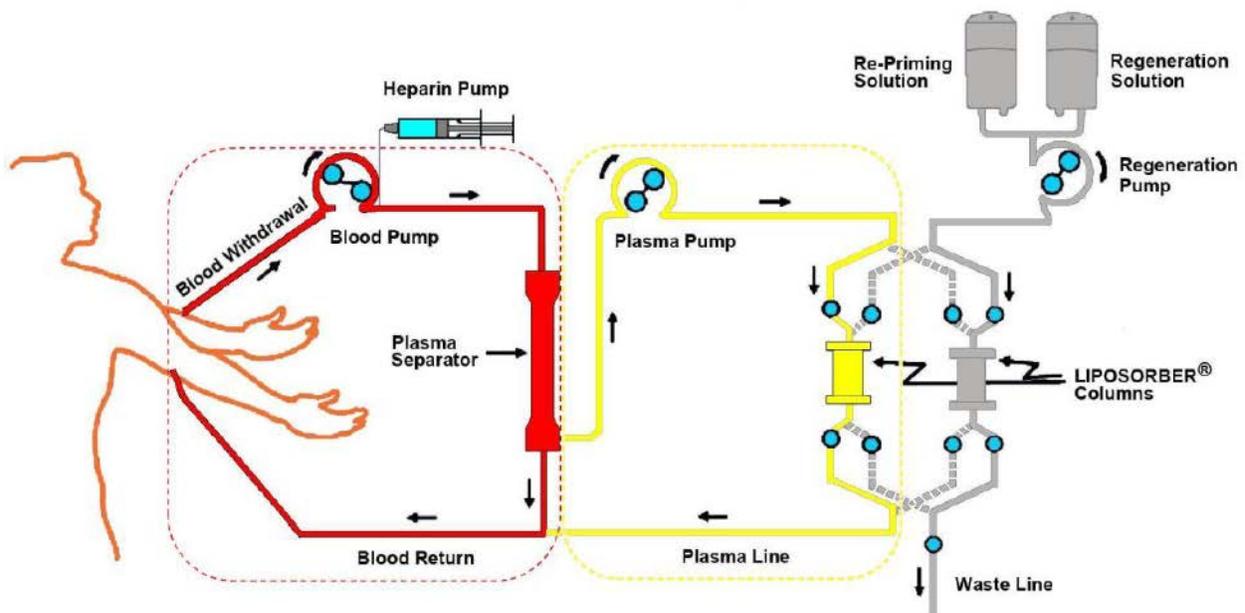


Figure 3. Schematic of Liposorber Extracorporeal Volume

VI. ALTERNATIVE PRACTICES OR PROCEDURES

There are several alternatives for the treatment of focal segmental glomerulosclerosis (FSGS). Each alternative has its advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle. Conventional management used in the treatment of FSGS prior to transplant include 1) use of corticosteroids such as prednisone, 2) use of cyclophosphamide or cyclosporine in patients refractory to prednisone therapy, and 3) renal transplantation. In addition, nutrition management with a diet low in protein and fat, fluid restriction, diuretics, and antihypertensive drugs are used to mitigate symptoms. Conventional management used in the treatment of FSGS after transplant include 1) use of corticosteroids such as prednisone, 2) use of cyclosporine, and 3) plasmapheresis. In addition, nutrition management with a diet low in protein and fat, fluid restriction, diuretics, and antihypertensive drugs are used to mitigate symptoms.

VII. MARKETING HISTORY

The Liposorber[®] LA-15 System has been commercially available in the US since 1996 (P910018) for familial hypercholesterolemia. It has also been used for the treatment of familial hypercholesterolemia (in adults and pediatrics) in Japan since 1986. In addition, the device was approved for marketing in Europe by TÜV SÜD as a Class IIb device in 1997 for similar indications. Table 1 lists year of approval in other countries.

Table 1. Marketing Approval Dates

Country	Year of Approval
The Netherlands	1987
Italy	1988
France	1989
Belgium	1990
Spain	1994
Germany	1995
CE Mark (TÜV)	1997
Canada	2012

The Liposorber[®] LA-15 System 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

1. Death
2. Cardiac (including myocardial infarction)
3. Thrombocytopenia
4. Infection/bacteremia
5. Hypersensitivity (anaphylactoid) reaction
6. Nausea and vomiting
7. Reduction in Vitamin E level
8. Transient decrease in serum protein and albumin level
9. Hypotension
10. Abdominal symptoms
11. Flushing/blotching
12. Angina/chest pain
13. Fainting/lightheadedness
14. Anemia
15. Prolonged bleeding (at cannulation site)
16. Hemolysis
17. Device malfunction
18. Vertigo
19. Diaphoresis
20. Urticaria
21. Shivering
22. Headaches

IX. SUMMARY OF PRECLINICAL STUDIES

The preclinical studies are supported by data reviewed under P910018 and its supplements because the device and materials are the same. Details for several of the non-clinical tests are as follows, but additional information can be found in P910018 and its supplements:

Biocompatibility Testing

The Liposorber[®] LA-15 System includes the following three (3) disposable device components: SULFLUX[®] KP-05 Plasma Separator, Liposorber[®] LA-15 LDL Adsorption Column, and Blood Tubing System for Plasmapheresis (NK-M3R). Biocompatibility tests were conducted on the patient-contacting materials in the device and included: cytotoxicity, hemolysis, muscle Implantation (3 day), animal and *in vitro* toxicological studies, immunological, sterility and pyrogenicity studies. The results showed the materials in the device to be safe for the intended use.

Bench Testing

The applicant conducted testing that evaluated the physicochemical properties of the materials used in the device. The following tests were conducted: column stability, mesh filter and column deterioration, hollow fiber deterioration, and package deterioration.

Shelf-Life Testing

The applicant conducted testing that established the minimum shelf-life for the components of the device. The following tests for the SULFLUX KP-05 Plasma Separator were conducted: pressure/leakage, extraction (appearance, foam extinction, UV absorption, and potassium permanganate (KMnO₄) reduction), membrane sealant, sterility, and biological (acute toxicity, pyrogenicity, intracutaneous reactivity, and hemolysis).

The following tests for the Liposorber[®] LA-15 Adsorption Column were conducted: pressure/leakage, extraction (appearance, foam extinction, pH, zinc, UV absorption, KMnO₄ reduction, nonvolatile residue, and heavy metals), sterility, biological (acute toxicity, pyrogenicity, intracutaneous reactivity, and hemolysis), and microparticle leakage.

The following tests for the tubing system were conducted: material strength (durability, elasticity), extraction (appearance, foam extinction, pH, zinc, tin, KMnO₄ reduction, UV absorption, nonvolatile residue, and heavy metals), sterility, biological (acute toxicity, pyrogenicity, intracutaneous reactivity, and hemolysis), and implantation.

The above tests established a shelf-life of 3 years for the SULFLUX[®] KP-05 Plasma Separator, 4 years for the LIPOSORBER[®] LA-15 Adsorption Column, and 2 years for the Tubing System for Plasmapheresis (NK-M3R).

Software Testing

Testing of the software included both functional and integration tests conducted throughout the entire development of the software. This includes the validation and verification testing and hazard analysis conducted on the finished device.

Emulation of the software evaluated the accuracy of (1) the transitions between operational modes, (2) the operations in the maintenance modes, and (3) the normal process modes, displays, sequence controls and alarms. Modular level testing of the software evaluated whether each module performed as designed. Bench testing of the device with water and bovine blood, which simulated actual patient treatment, was done under normal system operational conditions and sequences and under conditions that tested alarms for data inputs out of allowable ranges.

The results of the software testing showed that the software did perform according to specifications and that the design was appropriate for its intended use.

Electrical Safety Testing

The Liposorber[®] LA-15 System was tested by TÜV SÜD America, a Nationally Recognized Testing Laboratory recognized by OSHA, in accordance with IEC 60601-1, *Medical Electrical Equipment - Part 1: General Requirements for Safety*, 1988; Amendment 1, 1991-11, Amendment 2, 1995. In particular, the device was tested for insulation resistance, insulation strength, and current leakage.

The results of the tests showed that the device met the safety requirements of the above standards.

X. SUMMARY OF CLINICAL INFORMATION

Pediatric focal segmental glomerulosclerosis (FSGS) is a progressive and aggressive disease of the kidney that frequently leads to end stage renal disease (ESRD) in children. FSGS describes the histological changes that occur in the kidneys. Initially, development of areas of scarring (sclerosis) in some portions (segments) of the blood filtering units (glomeruli) of the kidney occurs. The disease is called “focal” since only some of the glomeruli are affected and “segmental” because often, only parts of the glomeruli are affected. As the disease progresses, more glomeruli develop sclerosis, and eventually, the sclerosis may fill the entire glomerulus. In addition, other areas of the kidney (tubules, interstitium) develop inflammation and sclerosis, and some tubules, which carry fluid within the kidney and absorb nutrients, are permanently damaged and lost (atrophy). As a result, the ability of the kidneys to filter the blood properly is lost, resulting in poor renal function.

FSGS is a histologic (tissue-based) diagnosis that may have no identifiable cause, in which case it is called primary FSGS. FSGS may also be secondary to another disease (e.g., hypertension, vesicoureteral reflux). The primary form of FSGS is more common among children and young adults, while secondary FSGS is more common in older adults. Regardless, the initial insult is thought to involve damage to the glomerular epithelial cells (podocytes), leading to protein leak, capillary expansion, formation of synechiae, and mesangial matrix proliferation. The primary laboratory finding of FSGS is proteinuria. Other findings are secondary to urine protein loss, and include hyperlipidemia, hypoalbuminemia, edema, and hypertension.

Treatment of primary FSGS is principally aimed at reduction of proteinuria. This can be

accomplished with the use of drugs that suppress the immune system, including corticosteroids, calcineurin inhibitors, and cytotoxic agents. Other medications that target renin-angiotensin-aldosterone system blockade (e.g., angiotensin converting enzyme inhibitors (ACE) and/or angiotensin receptor blockers (ARB)) decrease proteinuria and lower blood pressure which can slow the progression of proteinuric kidney diseases like FSGS. Nevertheless, spontaneous remission of primary FSGS is rare and the renal prognosis is poor, with FSGS patients frequently developing ESRD within 3-10 years. FSGS is much more likely to progress to ESRD than any other primary renal disease. For patients with primary FSGS who are refractory to standard treatments, there are generally no alternative options and progression to ESRD and lifelong renal replacement therapy (dialysis, transplant) is inevitable. Moreover, the lifespan of any child who develops ESRD is dramatically reduced, generally being 25-50 years.

The Liposorber[®] LA-15 System is for pediatric patients with primary FSGS only, since treatment of secondary FSGS primarily involves treatment of the underlying cause (e.g., hypertension).

The applicant did not conduct a prospective study regarding the proposed device for the intended populations. Instead, the applicant provided references for several studies of children with FSGS either before or after renal transplant who received therapy with the Liposorber[®] LA-15 System. Among the studies provided, all but two (2) (one including patients with FSGS treated with the device prior to transplant and one including patients with FSGS who received therapy after transplant) involved 1-2 patients. Only the larger studies were considered for analysis of the device for the intended populations.

Pre-transplant FSGS:

For the pre-transplant (FSGS) population, the applicant provided a published study (Hattori et al, 2003) which described the outcomes of eleven (11) children with steroid resistant primary FSGS who were treated unsuccessfully with conventional-dose cyclosporine therapy and showed persistent nephrotic range proteinuria. At the time of treatment with the Liposorber[®] LA-15 System, none of the patients had received a renal transplant (“pre-transplant”). At the start of the 7th apheresis treatment (average number of treatments: 11.5), prednisone was administered at a dose of 1mg/kg/d for 6 weeks, followed by a tapering schedule during subsequent months.

The effectiveness endpoint was the number of patients achieving remission of nephrotic syndrome. Other measures included renal function (i.e., glomerular filtration rate (GFR)), degree of proteinuria, cholesterol level and complications of therapy.

The criteria used to assess clinical response were:

- Remission of nephrotic syndrome (NS)
 - Complete remission: reduction in urinary protein ($< 4 \text{ mg/m}^2/\text{h}$) for 3 consecutive days with normal serum albumin and cholesterol levels, and stable renal function
 - Partial remission: lower urinary protein levels but persistent non-nephrotic proteinuria (protein $< 40 \text{ mg/m}^2/\text{h}$) with normal serum albumin
- Renal Function (as GFR, in $\text{ml}/\text{min}/1.73\text{m}^2$)
- Proteinuria ($\text{g}/\text{m}^2/\text{day}$).

Results:

Effectiveness:

- Achievement of remission (defined above) of nephrotic syndrome was observed in 7/11 patients (5 complete and 2 partial).
- Renal function (GFR) for the five (5) patients who achieved complete remission was normal during follow-up (median: 4.4 years, range: 4.0-11.1 years).
- Proteinuria declined in 7/11 patients (as evidenced by remission of nephrotic range proteinuria).

Safety:

Only one patient developed a complication (infection of the indwelling catheter used to receive the therapy).

Conclusion:

The authors suggest that combined LDL-apheresis and prednisone therapy can be a valuable therapeutic option for treating patients with steroid resistant FSGS. They also showed that patients with lower degrees of proteinuria and less advanced changes on renal biopsy prior to Liposorber treatment achieved higher rates of remission, lower levels of proteinuria and better preservation of GFR with therapy.

Post-transplant FSGS:

For the post-transplant FSGS population, the applicant provided a published study (Muso et al, 2007) of 41 patients with refractory FSGS. The study population included a sub-set of 7 patients (not defined but likely all adults) who developed recurrent FSGS after undergoing renal transplantation. The study was intended to evaluate the long-term outcome of LDL apheresis in patients with FSGS.

The study included the change in lab values (e.g., serum protein, serum albumin, proteinuria) at 1 month after treatment and measured the number of patients achieving remission of nephrotic syndrome at 2 and 5 years after Liposorber treatment. Although the investigators did not indicate that any of the patients included in the analysis were children, the results can be used to assess effectiveness in children as the course of the disease is sufficiently similar in both adults and children.

The criteria used to assess clinical response were:

- Remission of nephrotic syndrome (NS)
 - Complete remission
 - Type I incomplete remission: proteinuria negative or < 1.0 g/day and serum albumin > 3.0 g/dL
 - Type II incomplete remission: proteinuria < 3.5 g/day but serum albumin < 3.0 g/dL

Results:

Effectiveness:

- At 1 month after LDL apheresis total serum protein and albumin increased significantly and proteinuria was significantly decreased.

- Remission of nephrotic syndrome was observed in 18/29 patients followed at 2 years (62%).
- Remission of nephrotic syndrome was observed in 13/15 patients followed at 5 years (86%).

The seven (7) post-transplant patients were included in the 41 patients analyzed at 1 month and the authors did not analyze the data collected from pre- and post-transplant patients separately. Instead, the authors state that the exclusion of the post-transplant patient data did not impact the data trend or significance of the results, indicating that the post-transplant data were similar as a group to the pre-transplant patients in terms of increase in serum protein and albumin and decrease in proteinuria. The authors did not indicate the number of post-transplant patients included in the 2 and 5 year follow-up.

Safety:

The incidence of adverse events was not reported.

Conclusion:

The authors conclude that early administration of LDL-apheresis after the onset of nephrotic syndrome associated with FSGS provides a good long-term outcome.

An analysis was done to assess the safety of the device in children with familial hypercholesterolemia (FH) treated with the Liposorber[®] LA-15 system. The agency determined that risk data for children with familial hypercholesterolemia (FH) could be extrapolated to children with FSGS. See Section XI, Risk Probable Benefit Analysis, for further discussion. The following table displays the incidence of various adverse events in children with FH treated with the Liposorber[®] LA-15 system, as reported in two (2) published manuscripts (Stefanutti et al 2004 and Hudgins et al 2008):

Adverse Event (Side Effect)	How Often This Happens in Children Treated with the Liposorber LA-15 System for Another Disease (High LDL-Cholesterol) Due to the System Itself	Harm to You
Death	Not reported to occur	Death
Cardiac (heart-related, including abnormal heart rhythm, slow heart rate, fast heart rate and heart attack)	Not reported to occur	Mild to serious
Thrombocytopenia (low count of platelets that help blood clot and prevent bleeding)	Not reported to occur	Mild to serious
Infection (local or widespread)	Occurred in 2 of 20 patients	Mild to serious
Hypersensitivity (allergic-type reaction to a part of the system)	Not reported to occur	Mild to serious

Adverse Event (Side Effect)	How Often This Happens in Children Treated with the Liposorber LA-15 System for Another Disease (High LDL-Cholesterol) Due to the System Itself	Harm to You
Nausea and vomiting (abdominal symptoms)	0.3-2.5% of treatments (1/333 to 1/40 treatments)	Mild
Low Vitamin E level (which can cause muscle weakness, nausea and vomiting)	Not reported to occur	Mild
Temporary decrease in blood protein level (including albumin which holds water in the blood vessels)	Not reported to occur	Mild to moderate
Hypotension (low blood pressure)	2.0-2.5% of treatments (1/40 to 1/50 treatments)	Mild to severe
Flushing/blotching of skin	Not reported to occur	Mild
Angina (chest pain)	0.2-0.3% of treatments (1/500 to 1/333 treatments)	Mild to moderate
Fainting/lightheadedness	Not reported to occur	Mild to moderate
Anemia (low blood count)	Not reported to occur	Mild to serious
Prolonged bleeding at intravenous or catheter site	Not reported to occur	Mild to moderate
Hemolysis (breaking up of red blood cells)	Not reported to occur	Mild to serious
System (machine or its parts) malfunction	Not reported to occur	Mild to serious
Vertigo (dizziness, unsteadiness)	0-0.3% of treatments (none to 1/333 treatments)	Mild to moderate
Diaphoresis (excess sweating)	Not reported to occur	Mild
Urticaria	Not reported to occur	Mild
Shivering	0-0.3% of treatments (none to 1/333 treatments)	Mild
Headache	0-0.5% of treatments (none to 1/333 treatments)	Mild

XI. RISK PROBABLE BENEFIT ANALYSIS

Separate risk-probable benefit analyses are provided for the two (2) intended use populations: pre-transplant and post-transplant FSGS.

Pre-transplant FSGS:

The main probable benefit of treatment with the Liposorber[®] LA-15 System in FSGS patients without transplantation is delayed progression to end-stage renal disease (ESRD).

This would encompass delayed deterioration of renal function and severity of chronic kidney disease (CKD). Since CKD confers various complications, delayed progression of renal disease will reduce the impact of CKD complications including anemia, bone disease, poor linear growth, cardiovascular disease, and immune abnormalities. In addition, successful therapy with the device may permit reduction of exposure to and development of adverse events secondary to immunosuppression, including risk for serious infection, hypertension, anemia, electrolyte abnormalities (e.g., hypomagnesemia), hyperlipidemia, hair loss, reduced fertility, and chronic gastrointestinal disturbance.

There are several potential risks associated with treatment of children with FSGS either before or after transplant with the Liposorber[®] LA-15 System. In the Hattori et al study (2003) of children with FSGS prior to transplant treated with the device, only one (1) adverse event (catheter infection) was reported. The agency determined that risk data for children with familial hypercholesterolemia (FH) could be extrapolated to children with FSGS because they both exhibit a similar risk profile for many adverse events, including cardiovascular (e.g., hypertension, hypotension, myocardial infarction, arrhythmia), infection, and gastroenterological. The most common risks seen in 31 children with FH who received over 1,000 treatments with the Liposorber[®] LA-15 System included hypotension, abdominal discomfort, and dizziness (Stefanutti et al, 2004 and Hudgins et al, 2008). Cardiovascular disease (CVD)-related events including arrhythmia, bradycardia, tachycardia, and chest pain were also observed in children with FH. It should be noted that CV disease is generally more common and extensive in children with FH; therefore, CV risk in children with FH is a primary concern. In contrast, although CVD occurs in children with FSGS, it most commonly manifests at more advanced stages of CKD. For the proposed HDE, the device is not indicated for patients with advanced (Stage 3-5) CKD. Therefore, it is expected that CV risk may be less severe for children with FSGS than those with FH. Other procedure-associated risks that were uncommonly seen in children with FH include hemolysis, headache and anaphylaxis. Anaphylaxis or anaphylactoid reactions are either idiosyncratic or due to the use of angiotensin-converting enzyme inhibitors within 24 hours of treatment with the device. To mitigate that risk, a special warning is included in the labeling. The risk of infection exists, but the adverse event rate of infection was very low in children with FH. However, this risk can be mitigated by proper handling of the device and standard hygiene techniques. Moreover, this risk is likely not related to the device system itself but rather due to the requirement for vascular access (catheter) to conduct the procedure. Finally, there may be unanticipated adverse events associated with use of the device in children with pre-transplant FSGS, including decline in GFR due to immune-mediated or other unknown mechanisms.

In summary, children with FSGS prior to renal transplant are at high risk for progression of renal disease to ESRD. There are no cures for FSGS. Current therapies (mainly use of extensive immunosuppression medications) have proven inadequate for many patients and present risks that often outweigh benefits. There is preliminary evidence from one (1) study (Hattori et al, 2003) that treatment of some children with FSGS prior to transplant with the Liposorber[®] LA-15 System can induce remission, reduce proteinuria, and stabilize renal function in patients who would otherwise progress rapidly to ESRD. Data presented by Muso et al (2007) shows that Liposorber[®] LA-15 System therapy in

adults with recurrence of FSGS after transplant results in improvement in serum protein and albumin, and induction of remission in the majority of patients. Reduction of proteinuria is not only a marker of renal disease, but a mechanism to attenuate progression of inflammation and fibrosis, two (2) hallmarks of progressive disease. Preliminary evidence shows that treatment with the proposed device system in children with high risk for progression of FSGS provides potentially great benefit to some patients with a modest risk profile.

Post-transplant FSGS:

The main probable benefit of treatment with the Liposorber[®] LA-15 System post-transplant FSGS is the induction of remission of nephrotic syndrome (NS) that most commonly occurs in the first few months after transplant in children whose primary (original) renal disease was FSGS. Extracorporeal therapy (plasmapheresis and therapy with the Liposorber device) also has been shown to maintain or restore normal renal function. Amelioration of CKD is vital to help avoid progression to ESRD and return to dialysis, which itself presents heightened health risks. Moreover, since CKD confers various complications, delayed progression of recurrent renal disease will reduce the impact of CKD complications including anemia, bone disease, poor linear growth, cardiovascular disease, and immune abnormalities. There are several potential risks associated with treatment with the Liposorber[®] LA-15 System, including those outlined above for patients with pre-transplant FSGS. However, special attention is required for the risk of infection. As for children with pre-transplant FSGS, those with FSGS after transplant are at risk for catheter infection, but this risk is heightened in patients after transplant who will be receiving concomitant heavy and persistent immunosuppressive medications, even more so than that required prior to transplant.

In summary, children with FSGS after renal transplant (FSGS recurrence) are at high risk for progression of renal disease to ESRD. To date, the best therapy for post-transplant FSGS is extracorporeal (EC) therapy (plasmapheresis) combined with immunotherapy. However, plasmapheresis results in the removal and filtering of plasma which results in the indiscriminate removal of protective antibodies from the circulation. The Liposorber device involves the separation of plasma and the use of dextran sulfate cellulose adsorption columns that contain a microporous, hydrophilic gel composed of dextran sulfate cellulose beads, which have a strong affinity for apolipoprotein B-containing lipoproteins and remove LDL cholesterol from the plasma. The Liposorber device likely adsorbs other factors. Indeed, the data on children with FSGS who benefited from treatment with the Liposorber device strongly suggests that the device columns adsorb other circulating factors that either initiate or hasten the progression of FSGS. Therefore, treatment of children with FSGS with the Liposorber device may result in better clearance of toxins/factors that mediate the disease, with a lower risk profile than observed with plasmapheresis.

The Liposorber[®] LA-15 System has been marketed in the United States for patients with FH (P910018) and post-market data shows benefit (removal of LDL-cholesterol). The extensive safety data in children with FH can be extrapolated to children with FSGS. In summary, the Liposorber device may attenuate progression of renal disease in some children with FSGS while exposing the patients to a lower risk profile than extensive immunosuppression.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

This HDE was not taken to a meeting of the Gastroenterology-Urology Panel because it was determined that the preclinical and clinical issues raised by the HDE did not require panel review for the proposed indications.

XIII. CDRH DECISION

CDRH has determined that, based on the data submitted in the HDE, the Kaneka Liposorber[®] LA-15 System will not expose patients to an unreasonable or significant risk or illness or injury, and the probable benefit to health from using the device outweighs the risks of illness or injury, and issued an approval order on October 10, 2013.

The final conditions of the approval cited in the approval order are described below. This will include a prospective, multicenter, single arm post approval study with a total of 35 newly enrolled patients, treated at 3 to 10 clinical centers in the United States. The study participants will be followed for 24 months after the completion of the final apheresis procedure. The study visits will be as follows: Pre-procedural exams and laboratory tests, approximately 9 weeks of study apheresis procedures, and 1-, 3-, 6-, 12- and 24-month follow-up office visits. The primary objectives of this study are to confirm the safety and probable benefit of the Liposorber[®] LA-15 System in relieving nephrotic syndrome, defined as urine protein: creatinine ratio (Up/c) > 2.0 (gram protein per gram creatinine) with a first morning void urine sample, associated with refractory pediatric primary FSGS at 1 month after the final apheresis treatment. The primary probable benefit endpoint is the percent of patients who show complete or partial remission at 1 month after the final apheresis treatment. Complete remission is defined as Up/c < 0.2 (g/g) with a first morning void urine sample. Partial remission is defined as at least 50% reduction in Up/c compared to the value at screening or Up/c between 0.2 and 2.0 (g/g) with a first morning void urine sample. A sample size of 30 patients is required for this analysis. The primary safety endpoint is the rate of device-related and procedure-related serious adverse events (SAEs) occurring during the treatment period and up to 1-month follow-up visit. The rate of SAEs and corresponding 95% CI will be provided. The secondary objectives are to evaluate safety and probable benefit of the Liposorber[®] LA-15 System in relieving nephrotic syndrome associated with refractory pediatric primary FSGS at 3 months, 6 months, 12 months, and 24 months after the final apheresis treatment. The secondary safety and probable benefit endpoints include: nephrotic condition (complete remission, partial remission, and nephrotic state) including the percentage of patients who obtain complete and partial remission at 3, 6, 12, and 24 months; incidence of adverse events encountered during the period in which apheresis treatments are given; incidence of all adverse events and SAEs occurring within 3, 6, 12, and 24 months after the final apheresis treatment; and laboratory values, including eGFR at baseline, after the last treatment, and at 1, 3, 6, 12, and 24 months after the final apheresis treatment, including percent change from baseline and percentage of patients showing an increase or decrease in each value.

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

XIV. APPROVAL SPECIFICATIONS

Directions for use: See the Physician's Labeling.

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

Postapproval Requirements and Restrictions: See Approval Order.

XV. REFERENCES

1. Hattori M, et al: A Combined Low-Density Lipoprotein Apheresis and Prednisone Therapy for Steroid-Resistant Primary Focal Segmental Glomerulosclerosis in Children. *Amer J Kidney Dis* 42:1121-1130, 2003.
2. Hudgins L, et. al: Long-Term Safety and Efficacy of Low-Density Lipoprotein Apheresis in Childhood for Homozygous Familial Hypercholesterolemia. *The American Journal of Cardiology*. 102: 1159 – 1204, 2008.
3. Muso E, et al: Beneficial effect of low-density lipoprotein apheresis (LDL-A) on refractory nephrotic syndrome (NS) due to focal glomerulosclerosis (FGS). *Clin Nephrol*. 67(6):341-4, 2007.
4. Stefanutti C, et. al: Therapeutic apheresis in low weight patients: technical feasibility, tolerance, compliance, and risks. *Transfusion and Apheresis Science* 31: 3- 10, 2004.