

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:	PBM
Applicant's Name and Address:	Kaneka Pharma America LLC 546 Fifth Avenue, 22 nd Floor New York, New York 10036
Humanitarian Device Exemption (HDE) Number:	H170002
Humanitarian Use Device (HUD) Designation Number:	#17-379
Date of Humanitarian Use Device (HUD) Designation:	May 3, 2017
Date of Panel Recommendation:	N/A
Date of Notice of Approval to the Applicant:	March 20, 2018

Original PMA (P910018) for the LIPOSORBER® LA-15 System 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 ≥ 160 mg/dl* and either documented coronary heart disease or peripheral artery disease.

*The original indications for use was labeled as LDL-C ≥ 200 and documented coronary heart disease for Group C. The Summary of Safety and Effectiveness (SSED) for the original indication is available on the CDRH website:

http://www.accessdata.fda.gov/cdrh_docs/pdf/p910018.pdf. However, the indication for use was updated after approval of various supplements to the current indication:

P910018/S017

(<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P910018S017>),
P910018/S020

(<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P910018S020>),
and P910018/S021

(<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P910018S021>).

HDE H120005 for the LIPOSORBER® LA-15 System was approved on October 10, 2013 for the following indication:

This device 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 glomerular filtration rate (GFR) ≥ 60 ml/min/1.73m² or
- the patient is post renal transplantation.

The Summary of Safety and Probable Benefit (SSPB) to support the indication is available on the CDRH website: https://www.accessdata.fda.gov/cdrh_docs/pdf12/H120005B.pdf.

The current HDE was submitted to expand the indication for the Kaneka LIPOSORBER[®] LA-15 System to include adult patients with nephrotic syndrome associated with primary focal segmental glomerulosclerosis (FSGS) or for post-renal (kidney) transplantation recurrent FSGS, based on clinical literature evidence.

II. INDICATIONS FOR USE

The LIPOSORBER[®] LA-15 System is indicated for use in the treatment of adult and 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:

- patients who have been treated with angiotensin-converting enzyme (ACE)-inhibitors within the past 24 hours;

Severe anaphylactoid reactions including shock have been observed in patients treated with the LIPOSORBER[®] LA-15 System 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, when 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.

- 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;

- patients for whom extracorporeal circulation therapy with LIPOSORBER® LA-15 System 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
- 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, HDE 120005, and their 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.

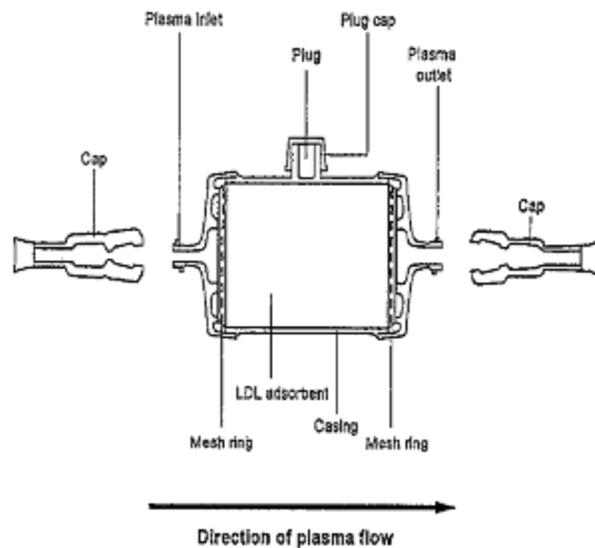


Figure 1. Schematic of Liposorber LA-15 Adsorption Column

The NK-M3R Tubing Set (approved on 3/31/2009 – Supplement 12 and 6/18/2010 – Supplement 13) 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 (H170002) and in H120005, the LIPOSORBER® LA-15 System 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 adults with FSGS indication is identical to the method of operation for both the original indication (P910018), to treat hypercholesterolemia in certain high risk patient populations, and for the pediatric FSGS indication (H120005). The method of operation is described below and Figure 2 contains 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 blood outlet port of 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.

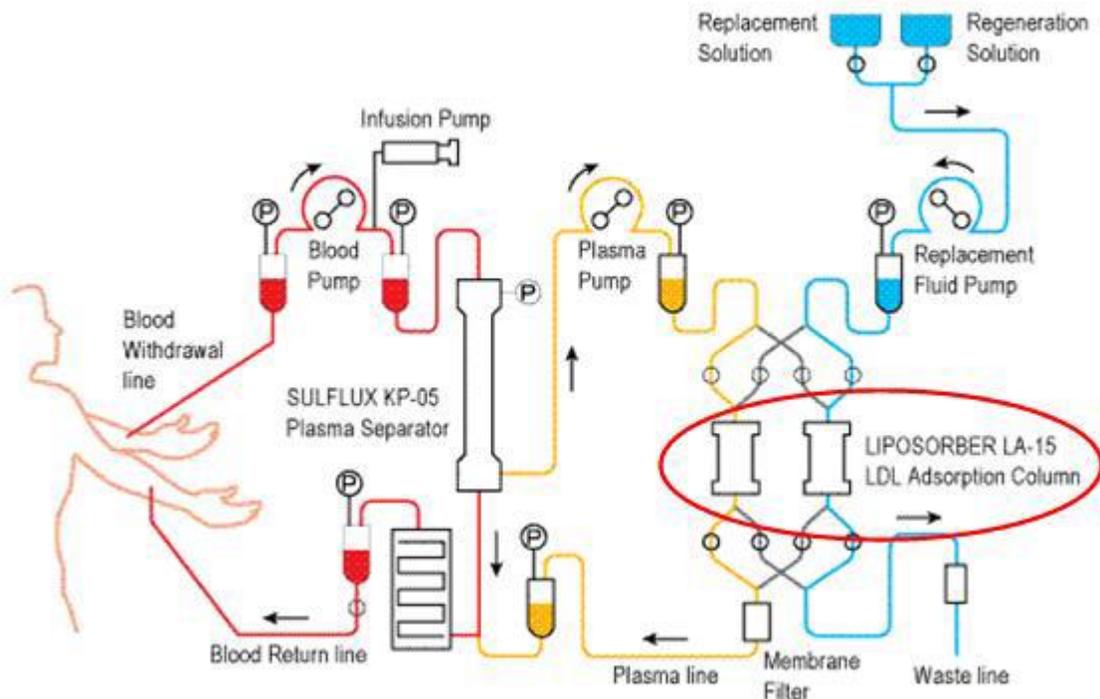


Figure 2. Schematic of Liposorber Operation

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 re-primed 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.

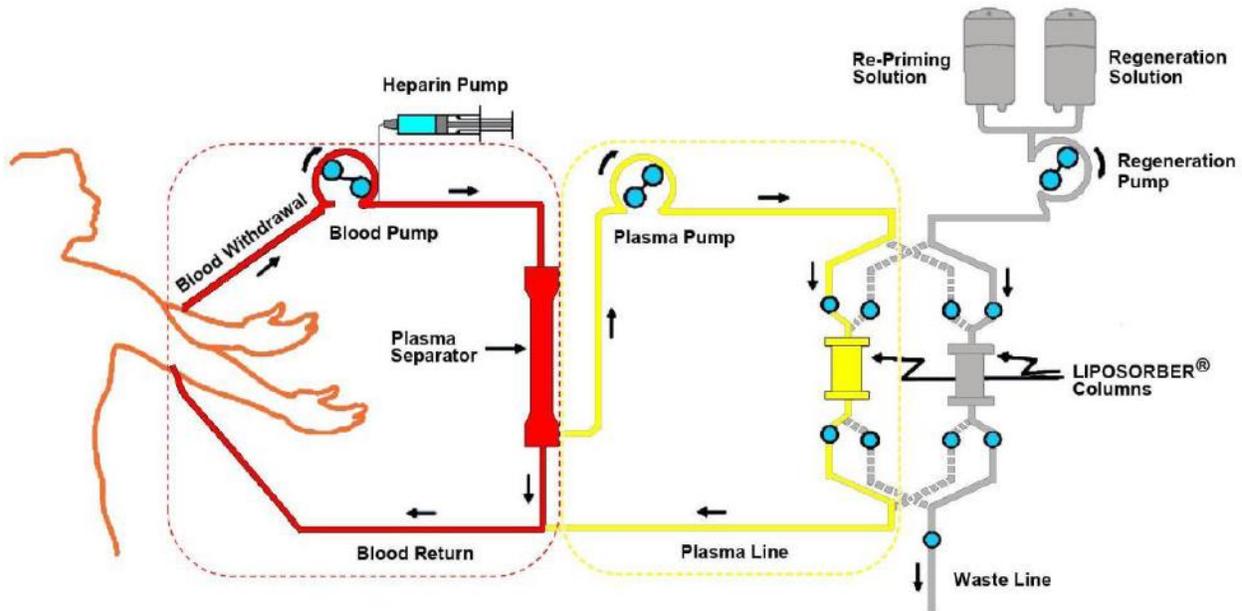


Figure 3. Schematic of Liposorber Extracorporeal Volume

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 the 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

In the U.S., the LIPOSORBER® has been approved for the treatment of pediatric FSGS patients since October 10, 2013.

The LIPOSORBER® LA-15 System has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. PROBABLE ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of probable adverse effects (i.e., complications) associated with the use of the device.

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

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

IX. SUMMARY OF PRECLINICAL STUDIES

The preclinical studies are supported by data reviewed under P910018 and its supplements since the device and materials are the same as those approved under the current HDE. Details for several of the non-clinical tests are as follows (and are identical to what was reviewed in H120005), 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

Background

Focal segmental glomerulosclerosis (FSGS) is an aggressive and progressive disease of the kidney that frequently leads to end stage renal disease (ESRD). 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 effected and “segmental” because often, only parts of the glomeruli are involved. 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.

Incidence of FSGS in Adults

As summarized in several articles and reviews, “primary FSGS has become one of the most common causes of idiopathic glomerular disease in adults. The incidence of primary FSGS has increased by 3- to 13-fold during the last 20-30 years, and the disease now accounts for 20%-25% of adult patients undergoing biopsy for evaluation of idiopathic glomerulonephritis (GN) [1-3]. Among adults undergoing biopsy for evaluation of idiopathic nephrotic syndrome, FSGS is now the most common lesion as well as, being seen in up to 35% of patients overall and in up to 80% of African American patients; that rate is two (2) to three (3) times the prevalence in white patients” [4-6].

Rosenberg and Kopp [7] showed that the prevalence of FSGS, relative to other glomerular disease diagnoses, seems to be increasing worldwide, and is a major contributor to ESRD. However, the absolute incidence and prevalence of FSGS are difficult to ascertain given the large global variations in the indications, accessibility, and pathology support for kidney biopsy. A population-based study in the southwestern United States examined 2501 adult kidney biopsies performed between the years 2000 and 2011. Over the 12 years studied, FSGS was the most common diagnosis (39% of biopsies), with an increasing incidence rate (from 1.6 to 5.3 patients per million). Although the average incidence rate was 2.7 patients per million, there was a significant racial/ethnic predilection. FSGS incidence rates are generally higher in men, being approximately 1.5-fold higher than in women.

Clinical Data

Clinical data to support the safety and probable benefit of LIPOSORBER® LA-15 System for FSGS in adults can be divided to pre-transplant FSGS and post-transplant FSGS. Note: The SSPB to support this indication in pediatrics is available on the CDRH website under the previously approved H120005:

https://www.accessdata.fda.gov/cdrh_docs/pdf12/H120005B.pdf.

Table 2 below outlines the clinical information FDA evaluated to support the addition of adults with FSGS to the indications for use originally approved in H120005. The sections following Table 2 provide further details of each study and FDA’s interpretation in support of the safety and probable benefit of the LIPOSORBER® LA-15 System for adults with FSGS.

Table 2 – Summary of Published Clinical Studies of LIPOSORBER® LA-15 System Treatment for Patients with Nephrotic Syndrome (NS) and FSGS in adults.

Study	No. of Patients	Study Design	Length of Follow-up	Clinical Outcomes	Pre-transplant or Post-transplant
Muso 2015 [11] Muso 2015 [12]	44 (26 with FSGS)	Prospective Multicenter Single arm	Immediate to 2 years after treatment	Urinary Protein (UP) decreased from 6.28 ± 2.96 to 3.46 ± 3.34 g/day.	Pre-transplant

Study	No. of Patients	Study Design	Length of Follow-up	Clinical Outcomes	Pre-transplant or Post-transplant
				21/44 patients (48%) had a favorable 2-years outcome.	
Muso 2001 [9] Muso 1999 [14]	17 (14 with FSGS)	Prospective Multicenter Controlled	Immediate to 2 years after treatment	UP decreased from 6.2 ± 3.3 to 2.7 ± 2.7 g/day. The rate of achieving complete or incomplete remission was 71%. As for the 2-years outcomes, 13/17 patients (76%) maintained UP <1.0 g/day.	Pre-transplant
Yokoyama 2002 [15]	6 (2 with FSGS; 1 treated with LIPOSORBER®)	Prospective Single Center	Unknown	This was a prospective study of the effects of lymphocytapheresis in treating various forms of NS in 6 patients. One patient with FSGS failed to respond to one month of LIPOSORBER® treatment.	Pre-Transplant
Nakamura 2006 [10]	8 FSGS	Prospective Single Center	2 weeks	UP decreased from 8.8 ± 4.2 g/day to 2.0 ± 1.2 g/day.	Pre-Transplant
Muso 2007 [13]	41 FSGS	Retrospective	5 years	At 1 month after LDL apheresis UP was significantly decreased. Remission of nephrotic syndrome was observed in 18/29 patients (62%) followed at 2 years and 13/15 patients (86%) followed at 5 years.	Pre-Transplant and Post-Transplant
Case Studies					

Study	No. of Patients	Study Design	Length of Follow-up	Clinical Outcomes	Pre-transplant or Post-transplant
Masutani 2005 [16]	1 FSGS	Case Report	1 year	LIPOSORBER® in conjunction with drug treatment resulted in reduction of UP from 6.8 g/day to 2.0 g/day. Incomplete remission had been maintained for more than 1 year.	Post-Transplant
Miura 2009 [19]	1 FSGS	Case Report	40 days	Six (6) cycles of hemodialysis were performed in conjunction with four (4) cycles of LIPOSORBER® treatment. UP and serum creatinine levels recovered to normal values, and UP became undetectable by 40 days post-treatment.	Pre-Transplant
Miyazono 2008 [18]	1 FSGS	Case Report	Unknown	After six (6) treatment sessions, the patient's UP decreased to non-nephrotic level. Furthermore, the patient's hypoproteinemia improved and renal function returned to normal. Although the patient experienced a relapse of nephrotic syndrome, six (6) more sessions of LIPOSORBER® treatment brought the UP down to 0.8 g/day.	Pre-Transplant
Tsukada 2006 [17]	1 FSGS	Case Report	Unknown	The patient underwent 8 sessions of treatment using	Post-Transplant

Study	No. of Patients	Study Design	Length of Follow-up	Clinical Outcomes	Pre-transplant or Post-transplant
				LIPOSORBER [®] , which resulted in the reduction of the UP level and improvement of renal functions.	
Haikal 2016 [20]	1 FSGS	Case Report	5 months	Partial remission sustained 5 months post therapy	Pre-transplant

Pre-transplant FSGS – Adults

- (i) **Muso et al. (2001) [8]**: This study describes the comparison of effectiveness between the treatment with the LIPOSORBER[®] LA-15 System in combination with steroids (LDL-A group) and that with steroids only (steroid monotherapy (SM) group) for patients with nephrotic syndrome who did not respond to full-dose (prednisolone, daily 1 mg/kg b.w.) therapy of 1-month duration under the fixed treatment protocol. The LDL group consisted of 17 patients (FSGS: 14, minimal change nephrotic syndrome (MCNS): 3) who were treated with the LIPOSORBER[®] LA-15 System. Treatments were performed twice a week for 3 weeks followed by weekly treatment for 6 weeks. The SM group included 10 patients (FSGS: 9, MCNS: 1) who were treated only with continuous full-dose steroids.

Results

Effectiveness:

- Total cholesterol (TC) level in the LDL-A group was significantly decreased after the treatment (337 ± 118 to 242 ± 45.2 mg/dL, $p=0.006$), whereas decrease of TC level in the SM group was not significant (448 ± 106 to 366 ± 159 mg/dL, $p=0.169$).
- Hypoalbuminemia significantly improved in the LDL-A group (2.7 ± 0.7 to 3.1 ± 0.7 g/dL, $p=0.014$), while almost no change was noted in the SM group (2.8 ± 0.4 to 2.9 ± 0.7 g/dL, $p=0.822$).
- Proteinuria was significantly ameliorated in the LDL-A group (6.2 ± 3.3 to 2.7 ± 2.7 g/day, $p=0.0008$), while significant amelioration of proteinuria was not observed in the SM group (8.7 ± 4.0 to 8.2 ± 7.7 g/day, $p=0.85$).
- Average duration needed for a decrease of urinary protein to <3.5 g/day was significantly shorter in the LDL group than in the SM group (14.7 ± 19.6 days vs 47.8 ± 6.9 days, $p=0.002$).
- At the end of the treatment period, 9 patients (52%) in the LDL-A group achieved urinary protein level <1.0 g/day, whereas only 1 patient (10%) showed the same level in the SM group.

- As for the long-term outcomes (2 years after the end of the treatment period), 13 out of 17 patients (76%) maintained urinary protein level <1.0 g/day in the LDL-A group, compared to only 2 in 9 patients (22%) in the SM group.

Safety:

The incidence of adverse events was not reported.

Conclusion

Superiority of therapeutic efficacy of the treatment with the LIPOSORBER® LA-15 System in combination with steroids to that with steroids alone was demonstrated in controlled study.

This study was a follow-up of the multicenter study reported by Muso et al [9]. In this study, the authors did not report any adverse events.

Summary: Among the 17 patients with FSGS, short-term and medium-term efficacy data were provided compared to controls. Adverse events were not mentioned in the report.

- (ii) **Nakamura et al. (2006) [10]**: This study investigated the effect of LIPOSORBER® LA-15 System in treating FSGS as part of a larger study to determine whether the levels of urinary liver-type fatty acid-binding protein (L-FABP) are associated with the severity of nephrotic syndrome. At the beginning of the study, all FSGS patients received 60 mg/day prednisone for 6 months, followed by either cyclophosphamide or mizoribine for another 6 months. Treatment with LIPOSORBER® LA-15 System was performed in eight (8) patients with drug-resistant FSGS twice a week for 3 weeks, then once a week for 6 weeks. In each 3-hour treatment session, 3000-4000 mL of plasma were treated. Renal function in terms of daily urinary protein excretion and serum creatinine levels were measured before the start of treatment and 2 weeks after the final treatment session.

Results

Effectiveness:

- Comparing the clinical parameters before and after the treatment, urinary protein and serum creatinine decreased significantly from 8.8 ± 4.2 g/day to 2.0 ± 1.2 g/day ($p < 0.01$) and from 123.8 ± 26.5 $\mu\text{mol/L}$ to 97.2 ± 17.7 $\mu\text{mol/L}$ ($p < 0.05$), respectively, and total protein increased from 40 ± 8 g/L to 60 ± 9 g/L ($p < 0.01$).
- In addition, serum level of L-FABP decreased from 122.6 ± 78.4 $\mu\text{g/gCr}$ to 64.4 ± 43.8 $\mu\text{g/gCr}$ ($p < 0.05$).

Safety:

The article did not report any adverse events associated with LIPOSORBER® LA-15 System.

Conclusion

This study demonstrated that LDL apheresis therapy with LIPOSORBER® LA-15 System ameliorated proteinuria, hypoproteinemia, and renal function in drug-resistant FSGS.

This was a prospective study. Among the eight (8) patients with FSGS, encouraging short-term effectiveness data were provided. A control arm was not included in this study. Adverse events were not mentioned in the report.

(iii) **Muso et al. (2015) [11]**: The investigators conducted a prospective, observational, multi-center cohort study (POLARIS study). In the POLARIS study, patients with nephrotic syndrome who did not respond to primary medication were registered before starting the treatment with LIPOSORBER® LA-15 System and clinical effectiveness and safety were examined. A total of 58 patients (who underwent 64 treatments) were registered in the study. Of the 64 treatment regimens, 17 were excluded for various reasons, leaving 47 treatment regimens for 44 patients available for analysis. As for FSGS, 23 patients were registered and underwent a total of 26 treatments. Clinical data were collected at baseline and after treatment with LDL-apheresis based on 24-hour urinalysis. Lipid profiles and clinical parameters were compared between before and after the treatment.

Results

Effectiveness:

- TC (331.10 ± 113.25 to 210.38 ± 77.4 mg/dL; $p < 0.01$) and LDL-cholesterol (205.86 ± 100.84 to 92.37 ± 56.64 mg/dL; $p < 0.01$) levels were significantly decreased after device therapy, whereas the changes of triglyceride (TG) and HDL-cholesterol (HDL-C) were not significant.
- Hypoproteinemia (serum protein), hypoalbuminemia (serum albumin), and proteinuria (urinary protein) were significantly ameliorated immediately after treatment (4.42 ± 0.69 to 4.68 ± 0.81 g/dL; $p < 0.05$, 2.15 ± 0.63 to 2.63 ± 0.79 g/dL; $p < 0.01$, and 6.28 ± 2.96 to 3.46 ± 3.34 g/day; $p < 0.01$, respectively). In addition, renal function (creatinine clearance) significantly improved immediately after treatment (58.59 ± 41.35 to 65.11 ± 41.39 mL/min; $p < 0.05$).
- Serum levels of fibrinogen and thrombin-antithrombin III complex (TAT) level were significantly reduced (374.46 ± 130.04 to 297.92 ± 108.87 mg/dL; $p < 0.01$, 16.39 ± 33.60 to 12.21 ± 34.10 ng/mL; $p < 0.05$, respectively) suggesting that treatment with LIPOSORBER® LA-15 System exerts anticoagulation activity.

Safety:

The incidence of adverse events was not reported.

Conclusion

LDL apheresis therapy with LIPOSORBER® LA-15 System rapidly ameliorated symptoms of nephrotic syndrome (i.e., proteinuria and hypoproteinemia, in more than half of the patients who failed to respond to primary medication).

This was a short-term study. The endpoints were:

- Complete remission: Urinary Protein (UP) = undetectable
- Incomplete Remission I: $UP < 1.0\text{g/day}$
- Incomplete Remission II: $1.0\text{ g} \leq UP < 3.5\text{ g/day}$
- No effect: $UP \geq 3.5\text{ g/day}$

In this study, complete or incomplete remission were considered favorable outcomes. The average number of apheresis sessions was 9.6/patient. An average of 3.5 L of plasma was treated per session. Among the 44 patients, FSGS was the diagnosis in 23 (52.3%) of the patients.

(iv) **Muso et al. (2015) [12]**: The long-term (2 years) outcome of the POLARIS cohort was investigated for the 44 subjects. Of the 58 patients who were registered in the POLARIS study, five (5) were excluded from the study because of protocol violation or inadequate data collection, six (6) were lost to follow up, and three (3) died during the follow-up period, thus leaving 44 subjects eligible for analysis at 2 years. As for primary diseases of the subjects, FSGS was found in the majority of cases, presenting in 28 subjects (63.6%).

Results

Effectiveness:

- Twenty-one (21) of the 44 subjects (47.7%) had a favorable outcome, with 11 subjects (25%) in complete remission (defined as urinary protein undetectable) and 10 subjects (22.7%) in incomplete remission I (defined as urinary protein level $< 1.0\text{ g/day}$). Twenty-three (23) subjects (52.3%) had an unfavorable result, with 11 (25%) in incomplete remission II (defined as $1.0\text{ g/day} < \text{urinary protein} < 3.5\text{ g/day}$) and 12 (27.3%) with no effect (defined as urinary protein level $> 3.5\text{ g/day}$).
- An analysis was performed of the factors affecting outcome. The authors found that the urinary protein level post-treatment was strongly associated with 2-year outcome ($p < 0.001$). For subjects with favorable outcomes, the urinary level after treatment was $1.68 \pm 1.76\text{ g/day}$ compared to $6.18 \pm 3.24\text{ g/day}$ for subjects with unfavorable outcomes.
- Improvement of parameters representing disease conditions of nephrotic syndrome, including serum albumin, estimated glomerular filtration rate (eGFR), urinary protein, and total and LDL cholesterol were all significantly associated with favorable outcome. This suggests that an early rapid alleviation of nephrotic syndrome by LDL-apheresis contributes to a favorable outcome.

Safety:

No adverse event associated with LIPOSORBER[®] LA-15 System was reported in this report.

Conclusion

The POLARIS study demonstrated that LDL apheresis therapy with LIPOSORBER[®] LA-15 System ameliorates nephrotic conditions and that the therapeutic effectiveness of LDL apheresis was largely maintained for 2 years.

During the time from the short- to long-term POLARIS study, three (3) subjects died of diseases unrelated to NS (cerebral infarction, lung cancer, and pneumonia). Given the variety of histological diagnoses in the patients included in the study, it was challenging to ascertain the outcomes for patients with FSGS versus those with other diseases. That said, the study does report that urine protein levels decreased significantly and similarly for patients with/without FSGS and this study provides reasonable assurance of effectiveness of the device in about 50% of patients with FSGS.

Post-transplant FSGS - Adults

(v) **Muso et al. (2007) [13]**: This study describes 41 patients with refractory FSGS. The study population included a sub-set of seven (7) patients 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.

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. 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 years 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.

This was a retrospective study. Patients had drug-resistant (persistence of proteinuria ≥ 1.0 g/day after the initial treatment for at least 4 weeks) NS and FSGS. Of the 41 cases of NS due to FSGS, 20 were new onset. The device treatment was provided in conjunction with standard medications for FSGS/NS: steroids, cyclosporine A, or other immunosuppressive medications. Each patient received 3-12 treatments with the device. Adverse events (safety) were not assessed.

In summary, among the 41 patients, encouraging 2-year efficacy data were provided for 29 patients (assuming constant enrollment) and 5-year data were available for 15 patients. This may be due to steady enrollment throughout the study period.

- (vi) **Muso et al. (1999) [9]**: The investigators describe two (2) separate studies of the effectiveness of LIPOSORBER[®] in treating NS: a preliminary, retrospective study of eight (8) patients and a prospective, multicenter study of 17 patients. The results of the prospective, multicenter study are described in more detail in another published article [8] (see below for a summary of this study).

In the preliminary, retrospective study, eight (8) steroid-resistant NS patients (7 patients with FSGS and 1 patient with minimal change nephrotic syndrome) were treated with LIPOSORBER[®] in conjunction with steroid therapy. Prior to treatment initiation, all patients underwent a full dose steroid regimen for 1 month. LIPOSORBER[®] treatment was performed with different treatment protocols, with each patient receiving between two (2) and 13 sessions of LIPOSORBER[®] treatment.

LIPOSORBER[®] treatment resulted in an amelioration of nephrotic proteinuria and elevation of serum protein levels. At 2 weeks after the final LIPOSORBER[®] treatment session, complete remission (UP < 3.5 g/day and serum albumin > 3.0 g/dl) was achieved in five (5) patients (4 FSGS and 1 minimal change nephrotic syndrome) and incomplete remission (UP < 3.5 g/day and serum albumin < 3.0 g/dl) was achieved in one of the same FSGS patients who previously achieved complete remission but relapsed after 10 months. In five (5) of these six (6) patients, immunohistological study after the final LIPOSORBER[®] treatment showed a reduction in mesangial apoprotein B staining and a reduction in intraglomerular macrophage infiltration. The authors did not report any adverse events associated with LIPOSORBER[®] in this study.

In the multicenter study (17 patients with FSGS/NS), there was a significant decrease of UP and increase in serum albumin as well as a decrease of thromboxane (TXB2) excretion ($P < 0.05$) after the device treatment. The rate of achieving complete or incomplete remission was 71%. The authors did not report any adverse events.

- (vii) **Yokoyama et al. (2002) [14]**: This was a prospective study of the effects of lymphocytapheresis in treating various forms of NS in six (6) patients. Among the six (6) patients included in the report, one with FSGS and one with membranous nephropathy combined with FSGS showed a dramatic decrease of proteinuria and demonstrated a complete or partial remission following device therapy. One patient with FSGS failed to respond to one month of LDL apheresis therapy.

Summary of Supplemental Clinical Information

Below is a summary of data obtained from other pertinent studies, including small trials and case reports.

- (viii) **Masutani et al. (2005) [15]**: This study reported a case of a 47-year-old patient with biopsy-confirmed FSGS. The disease progressed to ESRD. He was then maintained on hemodialysis (HD) for 12 months before receiving a living-related renal transplant. Shortly after transplantation, the patient developed recurrent FSGS/NS and frequent episodes of acute rejection. The NS persisted even after the immunosuppressants were changed from cyclosporine A to tacrolimus (TAC), and from azathioprine to mycophenolate mofetil (MMF). The patient was then treated with plasma exchange for 12 sessions. Although the proteinuria transiently decreased from 8.9 g/day to 1.9 g/day, it increased to 7-8 g/day just 1 month after treatment. Twelve (12) sessions with LIPOSORBER[®] LA-15 System were performed in conjunction with TAC, MMF, and methylprednisolone. This treatment resulted in gradual reduction of proteinuria from 6.8 g/day to 2.0 g/day. Incomplete remission had been maintained for more than 1 year at the time of the manuscript. The authors did not report any adverse events associated with LIPOSORBER[®] treatment.
- (ix) **Tsukada et al. (2006) [16]**: This case study describes a 42-year-old patient who had recurrent FSGS after renal transplantation. Shortly after the transplant, proteinuria developed and GFR declined. The first renal biopsy indicated acute rejection; steroid pulse therapy and immunosuppressive agents failed to improve symptoms. A second biopsy revealed recurrence of FSGS. The patient underwent eight (8) sessions of treatment using the LIPOSORBER[®] LA-15 System, which resulted in the reduction of the UP level and improvement of renal function. No further recurrence of the disease or renal function deterioration was observed, and the patient was under follow-up observations on an outpatient basis. The authors did not report any adverse events associated with the treatment.
- (x) **Miyazono et al. (2008) [17]**: This case study describes a 73-year-old patient with collapsing FSGS. Although steroids/cyclosporine (CyA) initially reduced proteinuria, the patient's UP excretion deteriorated shortly after. The patient was then treated with the LIPOSORBER[®] LA-15 System. After six (6) treatment sessions, the patient's UP excretion gradually decreased, reaching a non-nephrotic level. Furthermore, the patient's hypoproteinemia improved and renal function returned to

normal. Although the patient experienced a relapse of NS, six (6) more sessions of device treatment brought the proteinuria down to 0.8 g/day.

(xi) **Miura et al. (2009) [18]**: This case study describes a 61-year-old patient who had biopsy-confirmed FSGS. The patient responded well to his initial prednisone treatment, but later the UP increased to 12.4 g/day and urinary volume decreased to less than 600 mL/day, with declining GFR, all possibly due to bisphosphonate therapy. After discontinuing the oral bisphosphonate, six (6) cycles of HD were performed in conjunction with four (4) cycles of the LIPOSORBER® LA-15 System. UP and serum creatinine levels recovered to normal values, and UP became undetectable by 40 days post-treatment. The authors did not report adverse effects associated with device.

(xii) **Haikal et al. (2016) [19]**: Adult relapsing FSGS Maintained in Partial Remission Following Lipoprotein Apheresis: Case Study.

- 52 year-old man with steroid-dependent FSGS and NS
- Failed to achieve remission with medical therapy
- Received LA therapy (LIPOSORBER® LA-15 System) once/week for 12 weeks
- At start, urine protein-to-creatinine ratio (P/C) was 4.4
- Partial remission sustained 5 months post therapy

FDA Summary of Probable Benefit

In summary, the FDA believes that based on the studies described above, there is probable benefit of the device for some adults with FSGS. The data from larger, longer-term studies, most notably those performed by Muso and colleagues [8, 9, 11-13] show improvements in urine protein and achievement of either partial or complete remission in 25-50% of patients who previously had demonstrated treatment-resistant FSGS. Specifically, among patients with FSGS unresponsive to standard therapy who are treated with the LIPOSORBER® LA-15 System, urine protein levels (a marker of effective therapy and long-term kidney health) decreased significantly in about 50% of patients. In the POLARIS Study reported by Muso et al [8, 9, 11-13] that included a large (44 patients) cohort of patients followed for 2 years, almost 50% had a favorable outcome, with 21 subjects either in complete or partial remission, a marker of treatment success. Moreover, improvement of serum albumin and eGFR (also markers of improved kidney health) were significantly associated with a favorable outcome in the patients who achieved a partial or complete remission. The results from two (2) other studies (Nakamura [10] and Yokoyama [14]) confirm the probable benefit of the device to ameliorate the progression of FSGS in some patients who have limited options for therapeutic benefit. In addition, data from several smaller studies and case reports concur with the results from the larger studies. The mechanism of the effect of the LIPOSORBER® LA-15 System to attenuate progression of FSGS in some patients is uncertain. However, taken together, the performance data for the device to provide probable benefit for some patients with treatment-resistant FSGS is clear and clinically-significant.

FDA Summary of Safety

The studies above did not report reliable adverse event data. However, the safety data from adults with FH treated with the device can be extrapolated to safety for adults with

FSGS treated with the LIPOSORBER® LA-15 System. Table 3 below (data generated in P910018) demonstrates the rates of various adverse events in adults with FH treated with the LIPOSORBER® LA-15 System:

Table 3 - Adverse Events in Patients with Familial Hypercholesterolemia Treated with the LIPOSORBER® LA-15 System

Adverse Event	Episodes		Patients	
	Count	Rate	Count	Rate
Hypotension	41	0.8%	25	33.8%
Nausea/Vomiting	27	0.5%	14	18.9%
Flushing/Blotching	20	0.4%	9	12.2%
Angina/Chest pains	10	0.2%	8	10.8%
Fainting	9	0.2%	6	8.1%
Lightheadedness	7	0.1%	6	8.1%
Anemia	6	0.1%	6	8.1%
Abdominal discomfort	5	0.1%	3	4.1%
Numbness/Tingling	4	0.1%	4	5.4%
Tachycardia	4	0.1%	3	4.1%
Headache	3	0.1%	3	4.1%
Shortness of Breath	3	0.1%	2	2.7%
Hemolysis	3	0.1%	2	2.7%
Bradycardia	3	0.1%	2	2.7%
Itching/Hives	2	0.04%	2	2.7%
Blurred Vision	2	0.04%	2	1.4%

The data above show that the rates of serious adverse events, such as hypotension, angina/chest pain, and tachycardia/bradycardia, were relatively low considering the high-risk profile of the patient population.

Below is a list of specific, common risks for patients with FSGS with a discussion of why these risks would not be increased after therapy with the device.

Venous Thrombosis

With regard to venous thrombosis, FDA believes that based on the published literature [20, 21] showing that treatment with the LIPOSORBER® LA-15 System may result in removal of certain pro-coagulation factors, the risk for thrombosis would be reduced in patients with FSGS treated with the device. Therefore, FDA believes that the risk for venous thrombosis will not be increased with exposure to the device.

Infection

The risk of infection in patients with FSGS is generally low. Moreover, case study reports show that the rates of infection in patients with FH or FSGS treated with the LIPOSORBER® LA-15 System are very low. The most common source of infection of patients treated with the device will be associated with the use of a central venous

catheter (CVC). To mitigate this risk, each treating center will have a standard procedure to minimize and monitor for CVC infections (aseptic technique). Moreover, if an infection or bacteremia is suspected, culture of the catheter ports, in conjunction with peripheral culture (optional), along with antibiotics, if indicated, will be required as standard of care. Finally, the labeling already lists infection as a potential risk. FDA believes that infection is a definite risk for any patient with a CVC exposed to the device. Standard of care is adequate to mitigate this risk.

Renal Failure

There is no evidence from studies in children or adults with FH or FSGS that the device significantly increases the risk of acute kidney injury (AKI) or exacerbation of chronic kidney disease (CKD). The LIPOSORBER® LA-15 System selectively removes LDL-C and other positively charged atherogenic proteins and therefore, does not affect any elements clinically meaningful for FSGS patients, such as electrolytes and albumin. FDA believes that the risk for AKI or exacerbation of CKD is remote.

Edema

While patients with FSGS patients and nephrotic syndrome (NS) do develop edema since serum albumin is reduced in NS, the likelihood that edema will be exacerbated due to treatment with the LIPOSORBER® LA-15 System device system is low since the device does not selectively remove albumin.

Hyperlipidemia

While LDL-cholesterol (LDL-C) is elevated in many patients with FSGS, there are therapeutic options (e.g., statins) for hyperlipidemia. It should also be noted that since the device removes LDL-C, its levels should be reduced after therapy with the device system.

FDA Summary of Safety Clinical Data

FDA conducted a thorough review comparing the overall risk profiles, co-morbidities, and risk factors for adverse events in patients with FH and FSGS treated with the LIPOSORBER® LA-15 System. We believe that extrapolation of safety data from adults with FH to adults with FSGS is acceptable based on the similar risk profiles (if not higher in patients with FH) of the two (2) patient populations. Given that the rates of adverse events (see Table 3 above) were very low (0.1-1.0%) in patients with FH, the rates of adverse events for patients with FSGS is expected to also be very low. Moreover, given the similar, if not higher, risk profile of patients with FH compared to those with FSGS, one can anticipate that the rates and severity of the most serious risks (hypotension (0.8%); angina/chest pain (0.2%); shortness of breath (0.1%); hemolysis (0.1%); bradycardia (0.1%)) will be similar, if not lower, in patients with FSGS. In addition, FDA assessed if specific conditions seen in patients with FSGS, such as thrombosis, infection, and edema may be exacerbated by LIPOSORBER® LA-15 system therapy. Based on the pathogenesis of these conditions and the mechanism of the device therapy, FDA does not believe that these conditions will be worsened by the device. In summary, there is an acceptable predicted safety profile for patients with FSGS treated with the LIPOSORBER® LA-15 System.

Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population. Note: the pediatric indication was approved in H120005.

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. None of the clinical literature 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.

XII. RISK/PROBABLE BENEFIT ANALYSIS

A) Probable Benefit Conclusion

The FDA believes that there is probable benefit of the device for some adults with FSGS. The data from large, longer-term studies, most notably those performed by Muso and colleagues [8, 9, 11-13] show improvements in urine protein and achievement of either partial or complete remission in 25-50% of patients who previously had demonstrated steroid/other immunosuppressive resistant-FSGS. Specifically, among patients with FSGS unresponsive to standard therapy who are treated with the LIPOSORBER® LA-15 System, urine protein levels (a marker of effective therapy and long-term kidney health) decreased significantly in about 50% of patients. In the POLARIS Study reported by Muso et al [8, 9, 11-13] that included a large (44 patients) cohort of patients followed for 2 years, almost 50% had a favorable outcome, with 21 subjects either in complete or partial remission, a marker of treatment success. Moreover, improvement of serum albumin and estimated eGFR (also markers of improved kidney health) were significantly associated with a favorable outcome in the patients who achieved a partial or complete remission. In some patients, complete or partial remission of nephrotic syndrome, a marker of stabilized kidney health, lasted for up to 5 years. The results from two (2) other studies (Nakamura [10] and Yokoyama [14]) confirm the probable benefit of the device to ameliorate the progression of FSGS in some patients who have limited options for therapeutic benefit. In addition, data from several smaller studies and case reports concur with the results from the larger studies. Taken together, the data are clear and clinically-significant and support probable benefit.

The mechanism of the effect of the LIPOSORBER® LA-15 System to attenuate progression of FSGS in some patients is uncertain, but may be related to reduction of LDL-C levels and/or removal of pro-inflammatory factors such as cytokines and chemokines, all of which are elevated in the serum of patients with nephrotic syndrome. Regardless, for some patients with limited or no available options for disease abatement, the device offers the potential to ameliorate the progression towards end-stage renal disease.

B) Safety Conclusion

The rates and severity of risks of the LIPOSORBER® LA-15 System are likely to be similar to that seen in adults with FH exposed to the device. As noted above, FDA believes that safety data in adults with FSGS can be established by showing that safety data for adults with FH treated with the device can be extrapolated to safety for adults with FSGS treated with the LIPOSORBER® LA-15 System. Table 3 showed that the rates of serious adverse events, such as hypotension, angina/chest pain, and tachycardia/bradycardia, were very low in adults. They were relatively low considering the high-risk patient profile of patients with FH treated with the device. Therefore, one would anticipate a similar, low risk profile in adult patients with FSGS treated with the device.

In addition, FDA assessed if specific conditions seen in patients with FSGS such as thrombosis, infection, and edema may be exacerbated by LIPOSORBER® LA-15 system therapy. Based on the pathogenesis of these conditions and the mechanism of the device therapy, FDA does not believe that these conditions will be worsened by the device. Finally, the post-approval study (PAS) protocol will state that certain adverse events (e.g., exacerbation of hypertension, exacerbation of edema, infection) are included in the surveillance of adverse events.

C) Probable Benefit-Risk Conclusions

In summary, we believe that use of the device will not expose adults with FSGS to an unreasonable or significant risk of illness or injury. Existing data demonstrate that the probable benefit to health from the use of the device outweighs the potential risk of injury or illness from its use, taking into account currently available alternative forms of treatment (i.e., drug treatment or renal transplantation).

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 several studies in adults with FSGS that treatment with the LIPOSORBER® LA-15 System in some adults prior to or after renal transplant can induce remission, reduce proteinuria, and stabilize renal function in patients who would otherwise progress rapidly to ESRD.

1. Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and probable benefit of this device when used in accordance with the indications for use. Therefore, it is reasonable to conclude that the probable benefit to health from using the device for the target population outweighs the risk of illness or injury, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment when used as indicated in accordance with the directions for use.

XIII. PANEL RECOMMENDATION

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.

XIV. 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 March 20, 2018.

The final conditions of the approval cited in the approval order are described below.

The applicant will perform a post-approval clinical study of the LIPOSORBER® LA-15 System. The purpose of the post-approval study is to evaluate the long-term safety and probable benefit of the LIPOSORBER® LA-15 System for the treatment of patients who have FSGS with a GFR \geq 60 ml/min/1.73 mm² accompanied by nephrotic syndrome in which standard treatment options are unsuccessful or not well tolerated or for the treatment of post renal transplant patients with nephrotic syndrome associated with primary FSGS.

The applicant has agreed to modify the ongoing post-approval study that was required as a condition of approval for the pediatric indication (approved under H120005), to include 35 newly enrolled adult subjects (in addition to the requirement of 35 subjects for the pediatric indication). This will be a prospective, multicenter, single-arm study in 3 to 10 clinical centers in the United States.

The study participants will be followed for 24 months after the completion of the final LIPOSORBER® LA-15 System 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 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.

To address the condition of approval for the adult indication, you will enroll additional 35 adult subjects; a minimum of 30 adult subjects are required for the primary probable benefit 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% confidence intervals will be provided

for the adult subjects. The secondary objectives are to evaluate safety and probable benefit of the LIPOSORBER® LA-15 System in relieving nephrotic syndrome associated with refractory 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 data will be analyzed and presented separately for the pediatric and adult populations.

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

XV. 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.

Post-approval Requirements and Restrictions: See Approval Order.

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