FDA Executive Summary

Prepared for the
Spring 2023 review by the
FDA's Pediatric Advisory Committee

H120005
Liposorber® LA-15 System

TABLE OF CONTENTS

I. INTRODUCTION

In accordance with the Pediatric Medical Device Safety and Improvement Act, this review provides a safety update based on the postmarket experience with the use of the Liposorber® LA-15 System (hereafter referred to as Liposorber LA-15) from Kaneka in pediatric patients for the treatment of nephrotic syndrome associated with primary focal segmental glomerulosclerosis (FSGS) since approval in 2013.

As stated in section 520(m)(8) of the FD&C Act, the agency's Pediatric Advisory Committee will annually review all HUDs intended for use in pediatric patients that are approved on or after September 27, 2007, to ensure that the HDE remains appropriate for the pediatric populations for which it is granted.

The Liposorber LA-15 System, a blood processing system that is used outside the body, includes disposable components and a control/monitor unit. The device works by removing certain lipoproteins from the patient's blood. The patient's blood is first passed through a plasma filter where the blood cells are separated from plasma (the liquid component of the blood). The plasma is then further passed through two adsorption columns, which are packed with a gel designed to capture the lipoproteins in the blood. The blood cells and the treated plasma are then returned to the patient via the blood return line.

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 $\geq$ 60 ml/min/1.73m^2, or

- The patient is post-renal transplantation.

III. BRIEF 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 (for subgroups of patients with familial hypercholesterolemia (FH)) and its supplements. The Liposorber® LA-15 System consists of four major components: the Sulflux KP-05 Plasma Separator, Liposorber® LA-15 Adsorption Columns, NK-M3R Tubing Set, and MA-03 Machine.

While the Liposorber® LA-15 System (P910018) is labeled for either weekly or bi-weekly use when used to treat FH (depending on the patient's LDL-C levels), in the Humanitarian Device Exemption (HDE), the Liposorber (H120005) is indicated for up to 12 uses in 3 months (twice weekly for 3 weeks then weekly for 6 weeks) for treatment of FSGS.

IV. REGULATORY HISTORY

The Liposorber LA-15 System received designation as a Humanitarian Use Device (HUD) Designation on September 28, 2012, and on October 10, 2013, the HDE application was approved by the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA).

V. POSTMARKET DATA: ANNUAL DISTRIBUTION NUMBER

Section 520(m)(6)(A)(ii) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) allows HDEs indicated for pediatric use to be sold for profit as long as the number of devices distributed in any calendar year does not exceed the annual distribution number (ADN). On December 13, 2016, the 21st Century Cures Act (Pub. L. No. 114-255) updated the definition of ADN to be the number of devices "reasonably needed to treat, diagnose, or cure a population of 8,000 individuals in the United States." Based on this definition, FDA calculates the ADN to be 8,000 multiplied by the number of devices reasonably necessary to treat an individual. Since each Liposorber LA-15 system treatment regimen includes 12 treatments/patient, the total ADN is 96,000.

Section 613(b) of the Food and Drug Administration Safety and Innovation Act (FDASIA) states that an HDE holder of a HUD for which an HDE was approved prior to the enactment of FDASIA on July 9, 2012 may submit an HDE supplement (21 CFR 814.108) requesting an exemption from the profit prohibition for a HUD. On September 4, 2012, the firm requested a determination that the Liposorber® LA-15 System met the conditions of either subclause (I) or (II) under section 520(m)(6)(A)(i) of the FD&C Act, as amended by the FDASIA, so that the device might be sold for profit. The HDE supplement request was approved by the FDA on October 10, 2013.

Table 1 below provides the number of device components distributed by the firm for the calendar year 2022 in the United States

Table 1. Annual Distribution Number-11/01/2021-10/30/2022

Device	Total Sales
MA-03 Apheresis Machine	0
Liposorber® LA-15 LDL Adsorption Column (2 columns/shipment)*	138
Sulflux® KP-05 Plasma Separator	144
NK-M3R (U) Tubing System for Plasmapheresis	162

*Each shipment of adsorption columns contains two columns. Therefore, 138 shipments would include 276 columns.

VI. POSTMARKET DATA: POST-APPROVAL STUDY (PAS)

a. PAS Conditions of Approval:

The Liposorber HDE (H120005) was approved on October 10, 2013

The purpose of the PAS study is to evaluate the long-term safety and probable benefit of the Liposorber LA-15 System for the treatment of pediatric patients who have FSGS with an estimated Glomerular Filtration Rate (eGFR) ≥60 ml/min/1.73 m^2 accompanied by nephrotic syndrome in which standard treatment options are unsuccessful or not well tolerated or for the treatment of pediatric post renal transplant patients with nephrotic syndrome associated with primary FSGS.

This is a prospective, multicenter, single arm 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 then for 1-, 3-, 6-, 12- and 24-month follow-up office visits after the last apheresis treatment.

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.

b. PAS Study Status:

PAS study data was available from the nine year interim post-approval study report, received at the FDA on March 11, 2022.

The sponsor reported that Institutional Review Board (IRB) approval had been obtained for ten clinical sites, and twenty-five subjects had been enrolled since study inception (Table 2). The study was anticipated to have enrolled 20 subjects by September 2017, and enrollment was anticipated to be completed in August 2018.

Table 2. PAS Study: Subject Enrollment and Study Status

Interim Report	Date Received	Pediatric Sites Enrolled	Subejcts Enrolled	Study Status	Actions Taken by FDA
6-month	7/8/14	0	0	Study Pending	
12-month	10/2/14	0	0	Progress Adequate	
18-month	4/6/15	3	0	Progress Adequate	
24-month	10/1/15	3	4	Progress Adequate	
36-month	10/4/16	3	9	Progress Inadequate	• Worked with sponsor to revise study timeline • Provided recommendations for enrollment strategies
39-month	12/28/16	4	9	Progress Adequate	
48-month	10/13/17	6	14	Progress Inadequate	• Deficiency letter issued to request plan from sponsor for improving enrollment
60-month	10/09/18	7	14	Progress Inadequate	• A teleconference was scheduled with the sponsor to identify current enrollment barriers and alternatives to improve it.
72 month	09/12/2019 and 12/25/2019	7	17	Progress Adequate	
84 month	10/07/2020 and 12/28/2020	7	23	Progress Adequate	
96 month	10/06/2021	10	25	Progress Adequate	
101 month*	03/11/2022	13	25	Progress Adequate	

**Please note that the 2022 annual clinical report submission date was changed by the sponsor from October to March and was submitted 03/11/2022. Therefore, the current serial update covers the more cirucumscribed five-month period of data conveyed since the prior annual report. Updated clinical data was requested but not required at this time;no additional data has been received.*

Since the last report:

- No new subjects were enrolled
- One (1) subject (Subject V) reached the 24-month follow-up visit
- One (1) subject (Subject X) reached the 6-month follow-up visit

The distribution of subjects' demographics is presented in Table 4 below.

Table 4. Demographics of Enrolled Subjects (n=25)

	N	%
Age (years)		
6 - 8	7	28.0
9 - 11	6	24.0
12 - 14	7	28.0
15 - 17	2	8.0
18 - 20	3	12.0
Sex		
Male	12	48.0
Female	13	52.0
Race/ethnicity		
Caucasian	15	60.0
African American	6	24.0
Hispanic/Latino	2	8.0
Unknown	2	8.0

Source: Constructed based on data from H120005 annual reports

Subject enrollment and status and the reasons for withdrawal are exhibited in Table 5 below. Since study inception, there have been two protocol deviations (two subjects who should have been excluded from study entry due to not meeting inclusion criteria). Those two subjects are still undergoing follow-up visits, as well as two subjects who withdrew and then underwent a second round of treatment.

Summary of the report to date: Twenty-five (25) subjects have been enrolled since study inception. Among those:

- Three (3) subjects were excluded from the study due to protocol deviations
- Seven (7) subjects withdrew from the study after completing all device treatments without any further follow-up. Since the primary probable benefit endpoint required data one month after the final device treatment, these subjects had unevaluable benefit data.
- One (1) subject withdrew during the device treatment period
- There is evaluable probable benefit follow-up data for fourteen (14) subjects. Among those subjects:
  - Five (5) subjects completed all 24 month follow-up visits
  - Three (3) subjects are in active follow-up. Among those subjects:
    - One (1) subject has completed the six month visit

    - One (1) subject has completed the twelve month visit
- Four (4) subjects withdrew after the one month, post-treatment visit
- One (1) subject withdrew after the three month, post-treatment visit
- One (1) subject withdrew after the six month, post-treatment visit
- One (1) subject withdrew after the twelve month, post-treatment visit

These results are also displayed in tables 5 and 6 below.

Table 5. Subject Enrollment and Status

Subject/Subject ID	Completed All Apheresis Treatments?	Follow-up Status	Reason for Withdrawal/Comment
Subject A	Yes	Withdrew after 6 month follow-up visit	Subject moved to another hospital and had further treatment off the study.
Subject B	Yes	Withdrew after 3 month follow-up visit	Subject relapsed and had another treatment series off the study.
Subject C	Yes	Completed 24 month post-treatment follow-up	
Subject D	Yes	Withdrew after final apheresis treatment	Subject dropped out and was lost to follow-up.
Subject E	No	Excluded from the study (treatment was never started)	Subject was revealed to have thyroid disease after enrollment (Medical Exclusion Criteria #8)
Subject F	Yes	Withdrew after final apheresis treatment	Unknown
Subject G	Yes	Withdrew after final apheresis treatment	Moved to another location
Subject H	Yes	Withdrew after final apheresis treatment	Required second series of device treatments-Major protocol deviation
Subject I	Yes	Withdrew after final apheresis treatment	Unknown
Subject J	Yes	Excluded from the study but continuing active follow-up	The reported eGFR level at baseline was 39.8 ml/min/1.73m^2, which fell out of the inclusion criteria of an eGFR > 60 ml/min/1.73m^2.
Subject K	Yes	Completed 24 month post-treatment follow-up	None
Subject L	Yes	Withdrew after 12 month follow-up visit	None
Subject M	Yes	Excluded from the study but continuing active follow-up	The reported Up/c of ACH004 at baseline was 0.08, which indicated that the subject achieved complete remission before treatment and was

			considered be inappropriate for treatment.
Subject N	No	Excluded from the study	None
Subject O	Yes	Withdrew after 1 month follow-up visit (continuing active follow-up after second round of treatment)	The subject did not recover from nephrotic syndrome in the first round of treatment and then had another round of treatment.
Subject P	Yes	Withdrew after 1 month follow-up visit (continuing active follow-up after second round of treatment)	The subject did not recover from nephrotic syndrome in the first round of treatment and then had another round of treatment.
Subject Q	Yes	Completed 24 month post-treatment follow-up	None
Subject R	Yes	Withdrew after 1 month follow-up visit	None
Subject S	Yes	Withdrew after final apheresis treatment	Unknown
Subject T	Yes	Completed 24 month post-treatment follow-up	None
Subject U	Yes	Withdrew after 1 month follow-up visit	Unknown
Subject V	Yes	Completed 24 month post-treatment follow-up	None
Subject W	Yes	Completed 12 month post-treatment follow-up	None
Subject X	Yes	Completed 6 month post-treatment follow-up	None
Subject Y	Yes	Withdrew after final apheresis treatment	None

Source: Constructed based on data from H120005 annual reports

Table 6. Follow-up Visits Completed

*Study Visit Completed**	*Number of Subjects*
1-month	4
3-month	1
6-month	2
12-month	2
24-month	5

*Seven subjects withdrew after the final treatment without a one month follow-up visit, three subjects were excluded due to protocol deviations and one subject withdrew during the treatment period

Interim Results

Probable Benefit

Primary probable benefit endpoint for evaluable subjects: The primary probable benefit endpoint is the percent of subjects who show complete or partial remission at 1 month after the final apheresis treatment.

- At the one month follow-up visit, six of fourteen (43%) subjects in whom Up/c data was available at baseline and at the 1 month visit had achieved either partial (four subjects) or complete (two subjects) remission.

Further U p/c data:

- At either the 3 month or 6 month visit (whichever they were able to achieve), seven of nine (77%) subjects had complete or partial remission at the three or six month follow-up periods, while the other subjects (23%) had no remission (nephrotic syndrome, or NS, persisting).
- At the 12-month follow-up, five of seven (71%) subjects displayed either partial (3 subjects) or complete (2 subjects) remission, while two of seven (29%) subjects had persistent NS.
- At the 24-month follow-up, four of five (80%) subjects displayed either partial (1 subject) or complete (3 subjects) remission, while one of five (20%) subjects had persistent NS.

Secondary probable benefit endpoint: Percentage of subjects who show complete or partial remission at the 3, 6, 12, and 24 month follow-up visits after the final apheresis treatment. Detailed information regarding remission status for each subject is displayed in Table 7.

Table 7. Remission Status Based on Up/c Ratio

Subject ID	1-month	3-month	6-month	12-month	24-month	Status
Subject A	PR	PR	PR			Withdrew after 6 mo visit
Subject B	N/A: Absence of 1-month visit	NS				Withdrew after 3 mo visit
Subject C	NS	PR	CR	CR	CR	Completed study
Subject D	Data not applicable due to absence of 1-month follow-up visit					Withdrew after final apheresis treatment
Subject E	Data not applicable due to absence of 1-month follow-up visit					Excluded from the study (treatment was never started)
Subject F	Data not applicable due to absence of 1-month follow-up visit					Withdrew after the final device treatment
Subject G	Data not applicable due to absence of 1-month follow-up visit					Withdrew (moved and lost to follow-up) after the final device treatment

Subject H	Data not applicable due to absence of 1-month follow-up visit					Withdrew after the final device treatment
Subject I	Data not applicable due to absence of 1-month follow-up visit					Withdrew after final apheresis treatment
Subject J	Data not applicable due to absence of 1-month follow-up visit					Excluded from the study but continuing active follow-up
Subject K	PR	CR	PR	CR	CR	Completed study
Subject L	NS	NS	NS	NS		Withdrew after 12 mo visit
Subject M	Data not applicable due to absence of 1-month follow-up visit					Excluded from the study due to protocol deviation
Subject N	Data not applicable due to absence of 1-month follow-up visit					Excluded from the study due to protocol deviation
Subject O	Data not applicable due to protocol deviation					Excluded from the study due to protocol deviation
Subject P	Data not applicable due to protocol deviation					Excluded from the study due to protocol deviation
Subject Q	PR	PR	PR	PR	PR	Active
Subject R	NS					Withdrew
Subject S	Data not applicable due to absence of 1-month follow-up visit					Withdrew after final apheresis treatment
Subject T	N/A: Absence of 1-month visit	NS	NS	NS	NS	Active
Subject U	NS					Withdrawal
Subject V	CR	CR	CR	PR	CR	Completed study
Subject W	PR	NS	PR	PR	(-)	Active
Subject X	CR	CR	CR	(-)	(-)	Active
Subject Y	NS					Withdrew after the final device treatment

NS=Nephrotic Syndrome; PR=Partial Remisssion; CR=Complete Remission; N/A=Data Not available or Reported; (-)=Not Yet Followed-Up; [a] Gray shading indicates that data was not collected (i.e., missing

data or subject withdrew), and absence of shading indicates that data were or will be collected; PR defined as urine protein-to-creatinine ratio (U p/c) of 0.2-2 (g/g) or decrease in U p/c ≥ 50%, and CR defined as U p/c < 0.2 (g/g); Source: Constructed based on data from H120005 annual reports.

For subjects that completed the device treatment, had no protocol deviations, and had at least the one month follow-up visit, the changes in urine protein (assessed by urine protein-to-creatinine ratio) from baseline (pre-device treatment) to the most recent follow-up study visit are shown in Table 8 below. Eighteen of twenty-one subjects (86%) displayed either stabilization or decrease of urine protein (assessed by urine protein-to-creatinine ratio). The evidence for these subjects shows a trend towards stabilization or improvement of laboratory indices (Table 8).

Table 8. Up/c Values By Study Visit

Subject	Baseline Up/c	Last Up/c	Trend in Up/c
1	44	18	Decrease
2	8	6	Stable
3	6	0.4	Decrease
4	2	0.2	Decrease
5	2	4	Increase
6	5	4	Stable
7	4	5	Stable
8	1	0.3	Decrease
9	27	15	Decrease
10	5	3	Decrease
11	28	38	Increase
12	8	0.2	Decrease
13	29	0.6	Decrease
14	28	0.1	Decrease
15	33	11	Decrease
16	4	8	Increase
17	17	12	Decrease
18	2	3	Stable
19	8	7	Stable
29	10	9	Stable
21	9	9	Stable

Source: Constructed based on data from H120005 annual reports

While not a secondary endpoint, the Agency also conducted analysis of change in eGFR as a measure of renal function. For subjects that completed the device treatment and had at least the one month follow-up visit, the changes in eGFR from baseline (pre-device treatment) to the most recent follow-up study visit are also shown in Table 9 below. The table shows that among the

seventeen subjects who completed full device treatment and had at least one post-treatment visit with laboratory results, eGFR was stable or increased in 15/17 (88%) subjects.

Table 9. Renal Function (measured by estimated glomerular filtration rate) and other laboratory values by study visit

Subject	Baseline Up/c	Last Up/c	Trend in eGFR
1	62	84	Increase
2	89	79	Stable
3	85	100	Increase
4	171*	109	Stable
5	60	34	Decrease
6	85	130	Increase
7	153*	161	Stable
8	78	72	Stable
9	159	160	Stable
10	60	191	Increase
11	216*	131*	Stable
12	16	48	Increase
13	58	152	Increase
14	14	12	Stable
15	65	59	Stable
16	54	44	Decrease
17	31	35	Stable

Source: Constructed based on data from H120005 annual reports
*Baseline or last eGFR value was falsely elevatedfor age. These values were defaulted to be normal for age.

The Agency also conducted an analysis of the outcomes of data for the eleven (11) subjects who either did not attend the visit immediately after the last device (five subjects), or, only attended the visit after the last treatment (6 subjects) treatment but did not attend any of the 1, 3, 6, 12 or 24 month follow-up visits, to ascertain if the exclusion of the data from those subjects may have skewed the results. Table 10 below shows those results:

Table 10. Outcomes of Subjects Who Withdrew Early or Were Excluded From the Study

Urine Protein and eGFR	Number of Subjects	Interpretation of Effect of Device on Disease Status
Labs Not Available After Last Apheresis Treatment	5	Cannot Determine

Decrease in Urine Protein with Increase in eGFR	1	Positive Response
Urine Protein not Available with Increase in eGFR	2	Likely Positive Response
Increase in Urine Protein with Decrease in eGFR	1	Disease Progression
No Change in Urine Protein with Decrease in eGFR	1	Likely Disease Progression
Urine Protein not Available with Decrease in eGFR	1	Likely Disease Progression

These outcomes (three subjects with positive response and three with disease progression) are generally similar to that of the subjects for whom follow-up data is available.

Safety

Primary safety endpoint: device-related and procedure-related SAEs: The most common or serious adverse events with the Liposorber LA-15 system are listed in Table 11 below:

Table 11. Known Adverse Events Observed with the Liposorber LA-15 System

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. Flushing/blotching
11. Angina/chest pain
12. Fainting/lightheadedness
13. Anemia
14. Prolonged bleeding (at cannulation site)
15. Hemolysis
16. Device malfunction
17. Vertigo
18. Diaphoresis
19. Urticaria

As of the eight year report, 91 adverse events have been reported, with two new events reported during the most recent reporting period. Table 12 shows the most serious adverse events that have been observed. The events include gastrointestinal (nausea/vomiting/diarrhea/abdominal pain/ache), fever/infection, upper respiratory symptoms, headache, edema/anasarca, lightheadedness/fainting, hypotension, anemia, malaise, and weakness. The sponsor posits and the agency agrees that a great majority of these events are most likely related to the subjects' underlying conditions and/or the requirement for a central venous catheter for vascular access.

Table 12. Summary Table of Adverse Events

Adverse Event Type	Number of Events	Relationship to Device
Gastrointestinal (Nausea/ Vomiting/ Diarrhea/Ache)	10	None
Fever/Infection	17	2 (Unknown)
Upper Respiratory (Congestion/Pharyngitis)	8	None
Headache	7	None
Edema/Anasarca (Exacerbation)	8	None
Lightheadedness/Dizziness	3	None
Malaise	3	None
Hypotension	2	None
Leg cramps	2	None
Allergic reaction (mild)	2	None
Pancreatitis	2	None
Transplant rejection (in subject treated after renal transplantation)	2	None
Hyponatremia	1	None
Dehydration	1	None
Worsening of Nephrotic Syndrome	1	None
Pneumonia	1	None
Bacteremia	1	None
Anemia	1	None
Hematuria	1	None
Acute Kidney Injury	2	1 Possibly related; 1 Unrelated

Source: Constructed based on data from H120005 annual reports

FDA Conclusions About Probable Benefit and Safety:

Final conclusions remain limited due to the small number of subjects and a limited period of follow-up in many subjects. For the primary probable benefit (percentage of subjects who show

complete or partial remission by measuring the Up/c at the 1 month follow-up visit after the final apheresis treatment), six of eleven (55%) of subjects had achieved either partial or complete remission one month after the last device therapy. However, 7/11 (64%) of the subjects that reached either the 3, 6, 12 or 24 month follow-up visit achieved either a partial or complete remission. In comparison, seven of eleven (64%) pediatric patients in the study by Hattori et al. (Amer J Kidney Dis, 2003) showed either complete or partial remission one month after device therapy. Overall, the data show stabilization or improvement of eGFR over the follow-up period in the vast majority (88%) of subjects. While the follow-up period was brief for some subjects, the stabilization or improvement in eGFR suggests amelioration of progression may have occurred in some subjects. The rates and severity of adverse events have been relatively low considering the underlying subject risk profiles (chronic kidney disease with nephrotic syndrome) and the known risks associated with any extracorporeal therapy. The review team believes that the vast majority of adverse events were unrelated to the device, while three were possibly related. Enrollment has improved slightly; therefore, the study status has been changed to "Progress Adequate." In summary, the post-approval study has not raised any new concerns regarding safety or probable benefit at this time. The study progress will continue to be monitored. FDA has worked interactively with the sponsor and study investigators to identify barriers to study enrollment that may be ameliorated by changes in study design.

LITERATURE REVIEW

Purpose

The purpose of this literature review is to keep current the knowledge published regarding the safety and effectiveness of Liposorber in pediatric patients for the treatment of nephrotic syndrome associated with primary (FSGS).

Methods

FDA conducted a literature review of the pediatric use of Liposorber by Kaneka on December 13, 2022 including all publications written in English between January 1, 2022 to December 13, 2022 in PubMed, Embase and Google Scholar. Without any additional filters, three groups of search terms were used:

1. Kaneka, Liposorber, Drug-resistant Pediatric Primary Focal Segmental Glomerulosclerosis, and Low-Density Lipoprotein (LDL)-Apheresis, or LDL-A.
2. Liposorber, Child, Focal Segmental Glomerulosclerosis
3. Apheresis, Child, Focal Segmental Glomerulosclerosis

After reading the titles, abstracts, and full-texts, 4 articles were selected.

Results

Summaries of the selected articles are included below.

Al-Mousily et al: Liposorber® LA-15 system for LDL apheresis in resistant nephrotic syndrome patients. Pediatr Nephrol 37:585-592, 2022

This article is a case series of five children who received LDL-A for treatment of SRNS. Each subject received 12 sessions of LDL-A. One patient achieved CR and three achieved PR. One patient did not respond to therapy. Those who responded stayed in either CR or PR for extended periods of time. LDL-A was successful at significantly reducing LDL ($p < 0.001$), total cholesterol ($p < 0.001$), and triglyceride ($p < 0.001$). The authors concluded that LDL-A therapy significantly decreased lipid levels in these patients and induced either CR and PR in the majority of subjects.

FDA Comment: The data for this article seems to be derived from that provided in the annual reports for this HDE. No new information is provided. No concerns.

Al-Mousily et al: Low-density lipoprotein apheresis for recurrent focal segmental glomerulosclerosis post renal transplant in pediatric patients. J Clin Apher 37:411-414, 2022.

This article is a case series of two children who received LDL-A for treatment of SRNS after renal transplantation after having not responded favorably to pre-transplant LDL-A. Each subject received 12 sessions of LDL-A. Both patients exhibited long-term reduction of proteinuria.

FDA Comment: The data for this article seems to be derived from that provided in the annual reports for this HDE. No new information is provided. No concerns.

Hefsa Rashed Al Shamsi et al: Management of recurrent focal segmental glomerulosclerosis (FSGS) post renal transplantation. Transpl Rev 36:100675, 2022

This was a review article describing management of post-transplantation recurrence of FSGS. Twenty-three studies were included in the review. They report that prophylactic plasmapheresis (PP) did not show a reduction in recurrence of FSGS in 2/3 studies. Prophylactic rituximab (RTX) was shown to reduce recurrence of FSGS in one-study and case reports. Treatment of recurrent FSGS with PP showed responses ranging from 41% to 100%. Only one study did not show improvement with PP use as treatment having a 27% remission. Treatment with rituximab showed variable results, with reports showing remission ranging from 57% to 100%. The authors concluded that while prophylactic PP does not play a role in preventing recurrent FSGS, prophylactic RTX might prevent some cases of FSGS post-transplantation. PP and RTX, when used as a treatment after recurrence show variable response rates.

FDA Comment: This article shows some benefit for apheresis for the treatment of recurrent FSGS after transplant. The results may support a role of devices such as the Liposorber LA-15 system for recurrent FSGS. No concerns.

Uffing et al: Long-term Apheresis in the Management of Patients With Recurrent Focal Segmental Glomerulosclerosis After Kidney Transplantation. Kidney Int Rep 7:1424-1427, 2022

FDA Comment: This article shows some benefit for apheresis for the treatment of recurrent FSGS after transplant. The results may support a role of devices such as the Liposorber LA-15 system for recurrent FSGS. No concerns.

The authors describe a multicenter, international, retrospective case series to determine the clinical course of 27 adult patients with recurrent FSGS treated with long-term apheresis (>6 months), with other immunotherpay. Of 27 patients who received long-term apheresis, 23 (85%) achieved partial or complete remission at one point after treatment. At maximum, there were 5 patients (19%) who experienced graft failure, despite apheresis. Bacterial and/or viral infections were observed in 24 (89%) patients (89%).

FDA Comment: This article shows some benefit for apheresis for the treatment of recurrent FSGS after transplant. Most patients developed infections, but the precise role of apheresis versus other immunosuppression cannot be determined. The results support the potential role of devices such as the Liposorber LA-15 system for recurrent FSGS. No concerns.

FDA Summary Comments: The literature review provides few new insights that are relevant for the ongoing HDE PAS.

OVERVIEW OF MEDICAL DEVICE REPORTS (MDR) DATABASE

Strengths and Limitations of MDR Data
Each year, the FDA receives several hundred thousand MDRs of suspected device-associated deaths, serious injuries and malfunctions. The MDR database houses MDRs submitted to the FDA by mandatory reporters (manufacturers, importers and device user facilities) and voluntary reporters such as health care professionals, patients and consumers. The FDA uses MDRs to monitor device performance, detect device-related safety issues, and contribute to benefit-risk assessments of these products. MDR reports can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type
- Detect actual or potential device problems used in a "real world" setting/environment, including:
    - rare, serious, or unexpected adverse events;
    - adverse events that occur during long-term device use;
    - adverse events associated with vulnerable populations;
    - off-label use; and
    - use error

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use. Because of this, MDRs comprise only one of the FDA's several important postmarket surveillance data sources. Other limitations of MDRs and FDA's internal MDR database include:

- MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time, or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.
- Confirming whether a device caused a specific event can be difficult based solely on information provided in each report. Establishing a cause-and-effect relationship is especially difficult if circumstances surrounding the event have not been verified or if the device in question has not been directly evaluated.
- MDR data is subjected to reporting bias, attributable to potential causes such as reporting practice, increased media attention, and/or other agency regulatory actions.
- MDR data does not represent all known safety information for a reported medical device and should be interpreted in the context of other available information when making device-related or treatment decisions.

The MDR report was provided by Joann Fujikawa. The product codes searched were MMY and PBN.

MDR #1:
Report Number-2435151-2022-00001; Date-08-29-2022. "The patient's fifth Liposorber treatment was completed on 4/18/2022. The site reported no device issues or complications during treatment. The patient was hospitalized from 4/20/2022 to 4/23/2022 due to acute kidney injury and was released when recovered. Patient also was reported to have shortness of breath and chest pain which were assessed as not related to liposorber treatment by the physician. The acute kidney injury relationship to treatment with liposorber was assessed as unknown. However, the physician has continuing the patient on liposorber treatments."

FDAComment: This report provides scant information to enable a worthwhile assessment of any potential relationship between the device and episode of acute kidney injury (AKI), and even between the respiratory symptoms and the device. AKI is not a listed potential adverse event associated with the Liposorber device. The device is labeled to potentially cause hypotension, which, in turn, could result in renal hypoperfusion, but the limited clinical details do not allow an assessment of that potential cause of AKI.

MDR #2:
Report number-2435151-2021-00001; Date-08-11-2021. "A pediatric patient developed focal segmental glomerular sclerosis (FSGS) with steroid resistant nephrotic syndrome. A tunneled Catheter for blood withdrawing was placed at right internal jugular vein on august 29, 2017 for commencing LDL-apheresis using the Liposorber LA-15 system. The LDL-apheresis up to 9th on October 11 was conducted without any problem in out-patient basis. Since the patient had fever on the next day of 9th LDL-apheresis, she was admitted to the hospital for further examination and medication. Her WBC was 34,200/microliter and the result of the blood culture was Escherichia Coli positive, which was found to become negative after administration of antibiotics. The 12th LDL-apheresis, the final session, on October 25th was over without any problem. The attending physician was planning to discharge the patient after removing the catheter."

FDA Comment: This adverse event (infection of a central venous catheter, or CVC) is most likely due to the access, not the Liposorber device. CVC not uncommonly get infected. However, there is a slight possibility that the Liposorber device may have added to the risk of infection, potentially due to the unintended removal of immune substances. That is unproven though. Regardless, infection is listed among the known potential risks in the Liposorber labeling. This report raises no safety concerns with the device.

MDR #3:
Report number-2435151-2021-00003; Date-06-24-2021: "The patient is a 14 years old boy who has been treated by the LDL-apheresis with Liposorber LA-15 system approved as a humanitarian use device (HUD) for his treatment of recurrent nephrotic syndrome associated with focal segmental glomeruloscerosis (FSGS) post renal transplantation. He has developed anemia and received exogenous erythropoietin but this was not optimally effective. After his 17th treatments with the LDL-apheresis, his anemic condition worsened into grade 3 anemia (his hemoglogin level fell below 7 g/dL) and required a PRBC transfusion."

FDA Comment: This patient develpped progressive anemia while receiving LA-15 treatments. Anemia (due to blood loss) is a known and listed risk for the Liposorber device in the labeling. The mechanism for blood loss with the Liposorber device is uncertain.

MDR #4:
Report number- 3002808904-2022-00011; Date-09-16-2022: "The patient's fifth Liposorber treatment was completed on 4/18/2022. The site reported no device issues or complications during treatment. The patient was hospitalized from 4/20/2022 to 4/23/2022 due to acute kidney injury and was released when recovered. Patient also was reported to have shortness of breath and chest pain which were assessed as not related to Liposorber treatment by the physician. The acute kidney injury relationship to treatment with liposorber was assessed as unknown. However, the physician has continuing the patient on liposorber treatments."

FDA Comment: This report provides scant information to enable a worthwhile assessment of any potential relationship between the device and episode of acute kidney injury (AKI), and even between the respiratory symptoms and the device. AKI is not a listed potential adverse event associated with the Liposorber device. The device is labeled to potentially cause hypotension, which, in turn, could result in renal hypoperfusion, but the limited clinical details do not allow an assessment of that potential cause of AKI.

MDR #5:
Report number- 3002808904-2022-00015; Date-11-18-2022: "Patient at the 22 week of gestation. Initial bolus of approximately 3500 iu of sodium heparin (subsequent continuous infusion at 0,1 ml / hour). Start of treatment with blood flow 50 ml / min - plasma flow 15 ml / min. At approximately 50 ml of treated plasma onset of skin flushing, tachycardia and headache. This required zeroing the plasma pump and administering iv saline with regression of symptoms in about 5 minutes. The treatment then continued with extraction at 5-7% and blood flow of 30-

40 ml / min based on the clinical symptoms presented by the patient. At 700 ml of treated plasma sudden coagulation in the disposable. Premature termination of the treatment with blood / plasma loss."

FDA Comment: This patient was a pregnant woman who was presumably receiving LDL-A for the management of pre-eclamsia. Successful treatment of some patients with pre-eclampsia with LDL-A has been reported. This patient developed flushing, tachycardia, headache, and later, the circuit clotted. The patient symptoms are reported in the labeling. The clotting of the circuit likely occurred, in part, due to the slower blood flow. The report does not reveal any new issues with LDL-A.

FDA Summary Comment: These reports raise no new questions about the safety of the Liposorber device. The only event reported that is not in the device labeling is acute kidney injury, and that event is most likely due to another etiology.

VII. SUMMARY

FDA recommends:

1. Continued surveillance and will report the following to the PAC in fall 2023 or spring 2024:
    - Annual distribution number
    - PAS follow-up results
    - Literature review
    - MDR/MAUDE review