FDA Executive Summary

Prepared for the
Spring 2024 review by the
FDA's Pediatric Advisory Committee

H120005
Liposorber® LA-15 System

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I. INTRODUCTION

In accordance with the Pediatric Medical Device Safety and Improvement Act, this review provides a safety update based on the post-market 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. 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. POST-MARKET 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.

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.

Table 1 below provides the number of device components distributed by the firm for the calendar year 2022-2023 in the United States.

Table 1. Annual Distribution Number-11/01/2022-10/30/2023

Component device	Device distribution number for pediatric use	Device distribution number for adult use (FYI)	Total
MA-03 Apheresis Machine (newly installed in the reporting period)	2	6	8
LIPOSORBER LA-15 LDL Adsorption Column	108	438	546
SULFLUX KP-05 Plasma Separator	120	438	558
Tubing System for Plasmapheresis NK-M3R(U)/(UL)	174	618	792

*Each shipment of adsorption columns contains two columns. Therefore, 108 shipments would include 216 columns. Source: Table provided by sponsor via email on 10/31/23.

VI. POST-MARKET 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 ten-year interim post-approval study report, received at the FDA on October 31, 2023.

The study was anticipated to have enrolled 20 subjects by September 2017, and enrollment was anticipated to be completed in August 2018. As of the current report, 28 subjects have been enrolled, among whom 17 subjects had evaluable data after completion of the device therapy.

Table 2. PAS Study: Subject Enrollment and Study Status

Interim Report	Date Received	Pediatric Sites Enrolled	Subjects 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 will be 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	
120-month	10/31/2023	10	28	Progress Adequate	

Since the last report:

- Subject X reached 24-month follow-up point
- Subject Y withdrew from the study after 3-month follow-up
- Subject AA reached 6-month follow-up point
- Subject BB enrolled in the study and reached 3-month follow-up point

- One new patient (Subject BB) was enrolled during the reporting period resulting in a total number of 28 patients

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

Table 4. Demographics of Enrolled Subjects (n=28)

	N	%
Age (years)		
6 - 8	7	25.0
9 - 11	7	25.0
12 - 14	8	29.0
15 - 17	3	11.0
18 - 20	3	11.0
Sex		
Male	13	46.0
Female	15	54.0
Race/ethnicity		
Caucasian	15	54.0
African American	7	25.0
Hispanic/Latino	2	7.0
Not described	3	11.0

Source: Constructed based on data from H120005 annual reports

Subject enrollment, subject 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-eight (28) 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 seventeen (17) subjects. Among those subjects:
  - Six (6) subjects completed all 24-month follow-up visits
  - Two (2) subjects are in active follow-up. Among those subjects:
    - One (1) subject has completed the three-month visit
    - One (1) subject has completed the six-month visit
  - Four (4) subjects withdrew after the one-month, post-treatment visit
  - Two (2) subjects withdrew after the three-month, post-treatment visit
  - One (1) subject withdrew after the six-month, post-treatment visit

- Two (2) subjects withdrew or could not complete follow-up 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 without follow-up	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 without follow-up	Unknown
Subject G	Yes	Withdrew after final apheresis treatment without follow-up	Moved to another location
Subject H	Yes	Withdrew after final apheresis treatment without follow-up	Required second series of device treatments-Major protocol deviation
Subject I	Yes	Withdrew after final apheresis treatment without follow-up	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	Not applicable
Subject L	Yes	Withdrew after 12-month follow-up visit	Unknown
Subject M	Yes	Excluded from the study but continuing active follow-up	The reported Up/c 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. Protocol deviation (successive treatment not in protocol).
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. Protocol deviation (successive treatment not in protocol).
Subject Q	Yes	Completed 24-month post-treatment follow-up	Not applicable
Subject R	Yes	Withdrew after 1-month follow-up visit	Unknown
Subject S	Yes	Withdrew after final apheresis treatment without follow-up	Unknown
Subject T	Yes	Completed 24-month post-treatment follow-up	Not applicable
Subject U	Yes	Withdrew after 1-month follow-up visit	Unknown
Subject V	Yes	Completed 24-month post-treatment follow-up	Not applicable
Subject W	Yes	Completed 24-month post-treatment follow-up	Not applicable
Subject X	Yes	Completed 24-month post-treatment follow-up	Not applicable
Subject Y	Yes	Withdrew after 3-month follow-up visit	Unknown
Subject Z	Yes	Withdrew after final apheresis treatment without follow-up	Unknown
Subject AA	Yes	Completed 6-month post-treatment follow-up	Not applicable
Subject BB	Yes	Completed 3-month post-treatment follow-up	Not applicable

Source: Constructed based on data from H120005 annual reports

Table 6. Last Follow-up Visit

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

*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.

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.

Further Up/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, six of eight (75%) subjects displayed either partial (3 subjects) or complete (3 subjects) remission, while two of eight (25%) subjects had persistent NS.
- At the 24-month follow-up, six of seven (84%) subjects displayed either partial (2 subject) or complete (4 subjects) remission, while one of seven (14%) subjects had persistent NS.

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-	NS				Withdrew after 3 mo visit

	month visit					
Subject C	NS	PR	CR	CR	PR	Completed study
Subject D	Data not applicable due to absence of 1-month follow-up visit					Withdrew after final apheresis treatment without follow-up
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 without follow-up
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 without follow-up
Subject I	Data not applicable due to absence of 1-month follow-up visit					Withdrew after final apheresis treatment without follow-up
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-month 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	NS					Excluded from the study due to protocol deviation
Subject	NS					Excluded from the study due to protocol deviation
Subject	PR	PR	PR	PR	PR	Active
Subject	NS					Withdrew

Subject S	Data not applicable due to absence of 1-month follow-up visit					Withdrew after final apheresis treatment without follow-up
Subject	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	CR	Active
Subject X	CR	CR	CR	CR	CR	Active
Subject Y	PR					Withdrew after the 3-month follow-up visit
Subject Z						Withdrew after final apheresis treatment without follow-up
Subject AA	CR	PR				Completed 6-month post-treatment follow-up
Subject BB	NS	NS				Completed 3-month post-treatment follow-up

NS=Nephrotic Syndrome; PR=Partial Remission; 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 (Up/c) of 0.2-2 (g/g) or decrease in Up/c ≥ 50%, and CR defined as Up/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 (As of 2022 annual report; 2023 data not available)

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	0.1	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
20	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 (As of 2022 annual report; 2023 data not available)

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	125	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 elevated for 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 current report, 97 adverse events have been reported, with six (6) 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
Fever/Infection	17	2 (Unknown)
Gastrointestinal (Nausea/ Vomiting/ Diarrhea/Ache)	12	None
Edema/Anasarca (Exacerbation)	9	None
Upper Respiratory (Congestion/Pharyngitis)	8	None
Headache	7	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
Pneumonia	2	None
Acute Kidney Injury	2	1 Possibly related; 1 Unrelated
Hypertension	1	None
Hyponatremia	1	None
Dehydration	1	None
Worsening of Nephrotic Syndrome	1	None
Bacteremia	1	None
Anemia	1	None
Hematuria	1	None
Mouth sores	1	None

Source: Constructed based on data from H120005 annual reports

Safety Data in Adults with FSGS Treated with the Liposorber Device System

For this and future executive summaries, the review team requested safety data in adults with FSGS treated with the Liposorber device system. To that end, the sponsor provided the following table below:

Table 13: Adverse Events for Adult Patients with FSGS Treated with the Liposorber Device (in H170002)

	Classifi -cation	Treatment visit	Description of AEs/SAEs	Severity	Study action	Outcome	Hospit ali -zation	Relationship to treatment
#1	AE	AFTER APH. 6M	SINUS INFECTION	MODERATE	NONE	Resolved	-	No
#2	AE	AFTER APH. 12M	MUSCLE PAIN	MODERATE	NONE	Resolved	-	No
#3	AE	AFTER APH. 12M	ACID REFLUX ESOPHAGEAL	MODERATE	NONE	Resolved	-	No
#4	AE	AFTER APH. 12M	ANXIETY	MODERATE	NONE	Resolved	-	No
#5	SAE	AFTER APH. 12M	ECOLI URINARY TRACT INFECTION	MODERATE	NONE	Resolved	+	No
#6	SAE	AFTER APH. 12M	CLOSTRIDIUM DIFFICILE COLITIS	SEVERE	NONE	Resolved	+	No
#7	SAE	AFTER APH. 12M	SEPSIS	SEVERE	NONE	Resolved	+	No
#8	AE	APHERESIS4	CATHETER OCCLUSION	MODERATE	TBC	Resolved	-	No
#9	SAE	BEFORE APHER10	INFECTION	SEVERE	TBC	Not Resolved	TBC	No
#10	SAE	BEFORE APHER10	EMBOLISM AND THROMBOSIS VENA CAVA	SEVERE	TBC	Not Resolved	+	TBC
#11	AE	BEFORE APHER1	HEADACHE	MILD	NONE	Resolved	-	No

*TBC=To be confirmed

The FDA agrees with the attribution of all events. The only event for which attribution was not determined is the event (# 10) of embolism and thrombosis of the vena cava. This event may have been due to a central venous catheter, which is required for the device therapy. Event #8 (catheter occlusion) is also related to vascular access required for the device therapy but is not directly resulting from the device system. It is noteworthy that hypercoagulability is not listed as an adverse event in the Liposober system labeling, but CVC can clot if the dose of anti-coagulation for extracorporeal therapy is inadequate or if there is an inherent defect in the catheter. Pending further information about event #10, the other events listed in the table do not raise any new safety concerns. The FDA will request further information about this event from the sponsor.

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 one-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, 6/8 (75%) and 6/7 (84%) of the subjects that reached either the 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 minimally increased.

The FDA requested adverse event data in adults with FSGS treated with the Liposorber device system. The only event for which attribution was not determined in the initial report was an event of embolism and thrombosis of the vena cava (Event #10 in Table 13). Through email exchanges, the sponsor provided additional information to this reviewer on December 15, 2023. They stated: "I am reporting some detailed information about the adverse event #10. My colleague inquired with site coordinators in the investigation site in question for detailed information about #10 and the PI's decision on "Relation to treatment". We have confirmed that "Relation to treatment" for #10 is "Not related", which was "TBC (to be confirmed)" at the time of my previous email report. Based on the information obtained from the investigation site, Kaneka safety manager expressed his opinion that MDR is not applicable for this event. Although incomplete in some respects, this is all information on the adverse event #10 at this time. With your useful instructions and suggestions in mind, we will collect information on adverse events related to the investigation device (Liposorber LA-15) and will reflect them on the next PAS interim report, and also report back to you as needed.

This reviewer believes this event may have been due to the presence of a central venous catheter (CVC), which is required for the device therapy. Hypercoagulability is not listed as an adverse event for the Liposober system, but CVC can clot if the dose of anti-coagulation required for extracorporeal therapy with the device system is inadequate or if there is an inherent defect in the catheter. The other events occurring in adults do not raise any new safety concerns. The FDA will request further information about the event of embolism and thrombosis of the vena cava from the sponsor.

In summary, the post-approval study current reporting period does not raise any new concerns regarding safety or probable benefit at this time. The study progress will continue to be monitored. FDA will continue to work 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 7, 2023 including all publications written in English between January 1, 2023 to December 7, 2023 in PubMed, Embase and Google Scholar. Without any additional filters, three groups of search terms were used:

1. FSGS, Liposorber, Child: 0 reports
2. Focal Segmental Glomerulosclerosis, Liposorber, Child: 0 reports
3. Focal Segmental Glomerulosclerosis, LDL-A: 1 report
4. Focal Segmental Glomerulosclerosis, Low-Density Lipoprotein (LDL)-Apheresis: 2 reports
5. Apheresis, Child, Focal Segmental Glomerulosclerosis: 0 reports

After reading the titles, abstracts, and full-texts, 3 articles were selected.

Results

Summaries of the selected articles are included below.

Muso et al: Updated evidence of beneficial effect of LDL apheresis for refractory nephrotic syndrome due to a variety of causative diseases for nationwide and global approval. Ther Apher Dial 27:987-999, 2023

FDA Comment: This review summarized the therapeutic evidence of the beneficial effect of LDL-A accumulated to date and the mechanisms of action analyzed from multifaceted perspectives. Topics discussed included the role of LDL-A on management of hyperlipidemia, the latter a factor causing mesangial cell injury, the role of LDL-A on inflammation, and the role of LDL-A on proprotein convertase subtilisin/kexin 9 (PCSK9) levels, all factors that participate in disease progression. The review also includes summaries of major trials (K-FLAT and POLARIS studies) that showed favorable short- and long-term efficacy with LDL-A for patients with inadequate response to standard medical therapy. This review did not specifically mention the efficacy of LDL-A in children with FSGS other than the existence of the sponsor's post-market study. The review did not provide a discussion of the risks of LDL-A.

Shima et al: Low-density Lipoprotein Receptor Activities, Lipids, Apolipoprotein, and Clinical Course of Patients with Steroid-resistant Nephrotic Syndrome Treated with Low-density Lipoprotein Apheresis: A Case Series. Intern Med (Online available)

FDA Comment: This report includes three patients with steroid-resistant nephrotic syndrome who were treated with low-density lipoprotein apheresis (LDL-A). The patients also received concomitant drug therapy, including corticosteroids and cyclosporine. In all cases, the serum concentrations of LDL, total and high-density lipoprotein cholesterol, and triglycerides were significantly lowered following LDL-A administration. The focus of this report was to summarize the effect of LDL-A on reduction of proteinuria, a marker for disease activity, and to highlights the role of LDL-A on improvement of LDL receptor activity, which may be an additional mechanism in the control of FSGS. This review did not specifically mention the efficacy of LDL-A in children with FSGS other than the existence of the sponsor's post-market study. The review did not provide a discussion of the risks of LDL-A.

Miao et al: Efficacy of extracorporeal plasma therapy for adult native kidney patients with Primary FSGS: a Systematic review. Renal Failure 45:2176694

FDA Comment: This review assessed the efficacy of various extracorporeal therapies (plasmapheresis, immunoadsorption, LDL-A, and lymphocytapheresis for adults with primary focal segmental glomerulosclerosis (FSGS). They cited 18 studies with 104 patients with therapy-resistant or refractory primary native FSGS patients. The overall response rate was 56%, with long-term benefit of 46%. Of the 101 non-hemodialysis patients, 54% achieved remission, with 30% complete remission (CR) and 23% partial remission (PR). Of 31 patients who received plasmapheresis, the response rate was 65%; CR and PR rates were 27% and 37% in 30 non-HD patients. Of 61 patients treated with LDL-A, the response rate was 54%; CR and PR rates were 41% and 3% in 29 non-HD patients. Of 10 patients treated with immunoadsorption, the response rate was 40%. This review did not specifically mention the efficacy of LDL-A in children with FSGS other than the existence of the sponsor's post-market study. The review did not provide a discussion of the risks of LDL-A.

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 post-market 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.

Using the search words "Liposorber" and/or "Kaneka" and the procodes MMY and PBN for the period of 12/01/2022-12/01/2023, there were no MDR reports.

VII. SUMMARY

FDA recommends:

1. Request further information from the sponsor about the event of embolism and thrombosis of the vena cava in an adult patient with FSGS treated with the device system.
2. Continued surveillance and will report the following to the PAC in fall 2024:
   - Annual distribution number
   - PAS follow-up results
   - Literature review
   - MDR/MAUDE review