FDA Executive Summary

Prepared for the
Spring 2025 Review by the
FDA's Pediatric Advisory Committee

Liposorber® LA-15 System

(H120005)

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 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 AND 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 2023-2024 in the United States.

Table 1. Annual Distribution Number- 11/01/2023 – 10/31/2024

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 machines	2 machines	4 machines
LIPOSORBER LA-15 LDL Adsorption Column	120 pieces	438 pieces	558 pieces
SULFLUX KP-05 Plasma Separator	174 pieces	420 pieces	594 pieces
Tubing System for Plasmapheresis NK-M3R(U)/(UL)	156 pieces	654 pieces	810 pieces

Source: Table provided by sponsor via HDE annual report submitted on 12/06/2024

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 are 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 125-month interim post-approval study report, received at the FDA on March 13, 2024 which covers the time report of March 1, 2023 to February 29, 2024.

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, 27 subjects have been

enrolled among whom 5 subjects had evaluable data after completion of the device therapy.

Table 2. PAS Study: Subject Enrollment and Study Status

Interim Report	Date Received	Total Pediatric Sites Currently Enrolled	Total 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	
125-month	03/13/2024	8	27*	Progress Adequate	

***** 1 Pediatric patient reported incorrectly enrolled in the previous reports, therefore removed.

Since the last report:

- Subject X completed 24 month follow up.
- Subject AA reached 12 month follow up point.
- Subject BB was newly enrolled in the study and reached 6 month follow up point.
- One pediatric patient (Subject E) was incorrectly reported as an enrollment in the previous interim reporting periods of the post-approval study, and this patient's report was removed from the 2024 interim report resulting in a total number of 27 pediatric enrollments.

The distribution of subjects' demographic is presented in Table 3 below. Data available from the 125-month interim post-approval study report, received at the FDA on March 13, 2024 which covers the time report of March 1, 2023 to February 29, 2024.

Table 3. Demographics of Enrolled Subjects (n=27)

	N	%
Age (years)		
6 – 8	6	22.0
9 - 11	7	26.0
12 - 14	8	30.0
15 - 17	3	11.0
18 - 20	3	11.0
Sex		
Male	12	44.0
Female	15	55.0
Race/ethnicity		
Caucasian	15	55.0
African American	7	26.0
Hispanic/Latino	3	11.0
Not described/Other	2	7.0

Source: Constructed based on data from H120005 annual post-approval study report

Subject enrollment, subject status, and the reasons for withdrawal are exhibited in Table 4 below.

Since study inception, there have been protocol deviations and resulting patient exclusions from the study. Two subjects who should have been excluded from study entry due to not meeting inclusion criteria were included (Subjects J and M). And two subjects withdrew and then underwent a second round of treatment (as successive treatment option) but that is not a part of the protocol (Subjects O and P). One more patient was excluded since the patient did not complete the device treatments and withdrew during treatment for unknown reasons (Subject N).

Summary of the report to date: Twenty-seven (27) subjects have been enrolled since study inception. Among those:

- Three (3) subjects were excluded from the study due to protocol deviations (Subjects J, M,

N)

- 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 (Subjects D, F, G, H, I, S, Z).
- There is evaluable probable benefit follow-up data for fifteen (15) subjects. Among those subjects:
  - Six (6) subjects completed all 24-month follow-up visits (Subjects C, K, Q, T, V, X)
  - Four (4) subjects withdrew after the one-month, post-treatment visit (Subjects O, P, R, U)
  - Two (2) subjects withdrew after the three-month, post-treatment visit (Subjects B and Y)
  - One (1) subject withdrew after the six-month, post-treatment visit (Subjects A)
  - Two (2) subject withdrew or could not complete follow-up after the twelve-month, post-treatment visit. (Subjects L, W)
- Two (2) patients are currently undergoing active follow up and will hopefully have evaluable probable benefit data in the near future. Among those subjects:
  - One (1) subject (Subject BB) was enrolled in the study and has completed 6 month follow up
  - One (1) subject (Subject AA) has completed 12 month follow up

These results are also displayed in tables 4 and 5 below.

Table 4. Subject Enrollment and Status (from the 125-month interim post-approval study report, received at the FDA on March 13, 2024 which covers the time report of March 1, 2023 to February 29, 2024 as available from the sponsor's report)

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 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	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	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 treatment.	The subject did not recover from nephrotic syndrome in the first round of treatment and then had another round of treatment. Data from 2nd round of treatment not included in the study since protocol deviation (successive treatment not in protocol).
Subject P	Yes	Withdrew after 1 month follow up treatment.	The subject did not recover from nephrotic syndrome in the first round of treatment and then had another round of treatment. Data from 2nd round of treatment not included in the study since 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 12-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 12-month post-treatment follow-up. Actively being followed	Not applicable
Subject BB	Yes	Completed 6-month post-treatment follow-up. Actively being followed	Not applicable

Source: Constructed based on data from H120005 post-approval study report

*: This patient completed the 24-month follow up visit out of window at 27 months therefore that visit is excluded.
This patient doesn't have 24-month urine protein to creatinine ratio data available.

Table 5. Last Follow-up Visit (from the 125-month interim post-approval study report, received at the FDA on March 13, 2024 which covers the time report of March 1, 2023 to February 29, 2024.)

*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 (including one subject who 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, eight of fifteen (53%) subjects in whom Up/c data was available at baseline and at the 1-month visit had achieved either partial (five subjects- Subjects A, K, Q, W, Y) or complete (three subjects- Subjects V, X, AA) remission.

Up/c data for one patient (subject V) was derived from in-house measurement. If the in-house data is excluded, the rate of partial or complete remission comes to 47% (seven out of fifteen patients).

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 6.

Further Up/c data:

- At either the 3-month or 6-month visit (whichever they were able to achieve), eight of twelve (67%) subjects had complete or partial remission at the three- or six-month follow-up periods, while the other subjects (33%) had no remission (nephrotic syndrome, or NS, persisting).
- At the 12-month follow-up, seven of nine (78%) subjects displayed either partial (3 subjects) or complete (4 subjects) remission, while two of nine (22%) subjects had persistent NS.
- At the 24-month follow-up, four of five (80%) subjects displayed either partial (3 subject) or complete (1 subjects) remission, while one of five (20%) subjects had persistent NS.

Table 6. Remission Status Based on Up/c Ratio (from the 125-month interim post-approval study report, received at the FDA on March 13, 2024 which covers the time report of March 1, 2023, to February 29, 2024.)

Subject ID	1-month	3-month	6-month	12-month	24-month	Status
Subject A	PR	PR	PR			Withdrew after 6 month visit

Subject B	N/A: Absence of 1-month visit	NS				Withdrew after 3 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 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 due to protocol deviation
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 P	NS					Excluded from the study due to protocol deviation
Subject Q	PR	PR	PR	PR	PR	Completed Study
Subject R	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 T	N/A: Absence of 1-month visit	NS	NS	NS	NS	Completed study
Subject U	NS					Withdrawal
Subject V	CR	CR	CR	PR	CR	Completed study
Subject W	PR	NS	PR	PR	N/A	Completed study
Subject X	CR	CR	CR	CR	N/A	Completed study
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	N/A	CR	Not yet followed up	Completed 12-month post-treatment follow-up. Being actively followed.
Subject BB	NS	NS	Not yet followed up	Not yet followed up	Not yet followed up	Newly enrolled in the study. Underwent pheresis sessions. Completed 6-month post-treatment follow-up. Being actively followed.

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. Twelve of fifteen subjects (80 %) 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 7).

Table 7. Up/c Values by Study Visit (from the 125-month interim post-approval study report, received at the FDA on March 13, 2024, which covers the time report of March 1, 2023 to February 29, 2024.)

Subject		Last Up/c	
	Baseline Up/c		Trend in Up/c
A	44	18	Decrease
B	8	6	Stable
C	6	0.4	Decrease
K	2	0.2	Decrease
L	2	4	Increase
O	5	4	Stable
P	4	5	Stable
Q	1	0.3	Decrease
R	27	15	Decrease
U	28	38	Increase
V	8	0.2	Decrease
W	29	1	Decrease
X	28	0.1	Decrease
AA	12	0.2	Decrease
BB	15	17	Increase

Source: Constructed based on data from H120005 post-approval study 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 8 below. The table shows that among the fifteen subjects who completed full device treatment and had at least one post-treatment visit with laboratory results, eGFR was stable or increased in 14/15 (93%) subjects.

Table 8. Renal Function (measured by estimated glomerular filtration rate) and other laboratory values by study visit (from the 125-month interim post-approval study report, received at the FDA on March 13, 2024, which covers the time report of March 1, 2023 to February 29, 2024.)

Subject	Baseline eGFR	Last eGFR	Trend in eGFR
A	62	84	Increase
B	89	79	Stable

C	85	100	Increase
K	171*	109	Stable
L	60	34	Decrease
O	85	130	Increase
P	154*	161	Stable
Q	78	72	Stable
R	159	160	Stable
T	60	191	Increase
U	216*	131*	Stable
V	16	48	Increase
W	58	152	Increase
Y	48	44	Stable
BB	31	46	Increase

Source: Constructed based on data from H120005 post-approval study 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 ten (10) subjects who either did not attend the visit immediately after the last device treatment (five subjects), or, only attended the visit after the last treatment (5 subjects) 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 9 below shows those results:

Table 9. 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 for adequate comparison	4	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 10 below:

Table 10. 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, there were 81 adverse events in 19 pediatric patients and 37 serious adverse events in 17 pediatric patients, with fourteen (14) new events reported during the most recent reporting period (February1, 2023 to February 29, 2024). Table 12 shows that these 14 adverse events were likely not related to the treatment procedure or the device. Table 10 shows the most serious adverse events that have been observed. The events include gastrointestinal (nausea/vomiting/diarrhea, infection (COVID and pneumonia), edema hypertension, mouth sores, blood counts related (neutropenia, leukopenia, hypogammaglobulinemia), right arm thrombus. 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 11. Summary Table of Adverse Events

Adverse Event Type	Number of Events	Relationship to Device
Fever/Infection	19	2 (Unknown)
Gastrointestinal (Nausea/ Vomiting/ Diarrhea/Ache)	15	None
Edema/Anasarca (Exacerbation)	10	None

Upper Respiratory (Congestion/Pharyngitis)	8	None
Headache	7	None
Lightheadedness/Dizziness	3	None
Malaise	3	None
Hypertension	3	None
Pneumonia	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
Mouth sores	2	None
Acute Kidney Injury	2	1 Possibly related; 1 Unrelated
Leukopenia/ Neutropenia	2	None
Hyponatremia	1	None
Dehydration	1	None
Worsening of Nephrotic Syndrome	1	None
Bacteremia	1	None
Anemia	1	None
Hematuria	1	None
Hypogammaglobulinemia	1	None
Thrombus	1	None

Source: Constructed based on data from H120005 post-approval study reports

The Data Safety Monitoring Report which covers the period from February 1, 2023 to January 31, 2024 was submitted to the Data Safety Monitoring Board (DSMB) and reviewed on February 22, 2024. The DSMB members reviewed the report including the data of efficacy and safety of the treatment which were obtained from pediatric patients* and assessed the appropriateness of the study performance. They agreed that the study can continue along with the current study protocol.

* The study's protocol stipulates that the DSMB will review and deliberate the validity of the safety and efficacy data of the PAS in terms of the treatment for pediatric patients.

Table 12: Adverse events in pediatric patients from February1, 2023 to February 29, 2024

No.	Classifi-cation	Date of occurrence (MM-DD-YY)	Date of disappearance (MM-DD-YY)	Treatment visit	Description of AEs/SAEs	Severity	Study action	Outcome	Hospitali-zation	Relationship to treatment (Attending Physician)	Relationship to treatment (Kaneka)

#1	AE	06-06-2023	UK	Before Apheresis2	Right arm thrombus	Mild	None	Resolved	-	No	No
#2	SAE	06-11-2023	06-16-2023	Before Apheresis3	Pneumonia	Moderate	None	Resolved	+	No	No
#3	SAE	06-26-2023	06-27-2023	Apheresis7	Hypertension	Moderate	None	Resolved	+	No	No
#4	AE	07-03-2023	07-04-2023	Before Apheresis8	Leukopenia	Moderate	None	Resolved	-	No	No
#5	AE	07-03-2023	07-04-2023	Before Apheresis9	Hypertension	Moderate	None	Resolved	+(*)	No	No
#6	AE	07-09-2023	07-24-2023	Before Apheresis9	Mouth Sores	Mild	None	Resolved	-	No	No
#7	AE	07-10-2023	07-10-2023	Apheresis9	Nausea	Mild	None	Resolved	-	No	No
#8	AE	07-10-2023	07-10-2023	Apheresis9	Vomiting	Mild	None	Resolved	-	No	No
#9	AE	09-01-2023	N/A	After 1-month F/U	Edema	Mild	None	Not Resolved	-	No	No
#10	SAE	11-23-2023	11-27-2023	After 6-month F/U	Neutropenia	Moderate	None	Resolved	+	No	No
#11	AE	11-24-2023	12-23-2023	After 6-month F/U	COVID Infection	Moderate	None	Resolved	-	No	No
#12	AE	12-11-2023	12-28-2023	After 6-month F/U	Hypogammaglobulinemia	Moderate	None	Resolved	-	No	No
#13	AE	03-23-2023	UK	After 6-month F/U	COVID Infection	Mild	None	Resolved	-	No	No
#14	AE	05-00-2023	05-00-2023	After 6-month F/U	Diarrhea	Mild	None	Resolved	-	No	No

UK: Unknown, 00: Unknown Month, Date, or Year, N/A: Not Available, +(*): Planned hospitalization
AE #1 to 12 occurred in patient BB while AE# 13 and 14 occurred in patient AA.

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 Table 13 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	Hospitali-zation	Relationship to treatment
#1	AE	AFTER APH. 12M	ACID REFLUX ESOPHAGEAL	MODERATE	NONE	Resolved	-	No
#2	AE	AFTER APH. 12M	ANXIETY	MODERATE	NONE	Resolved	-	No

#3	SAE	AFTER APH. 12M	E.COLI UTI	MODERATE	NONE	Resolved	+	No
#4	SAE	AFTER APH. 12M	CLOSTRIDIUM DIFFICILE COLITIS	SEVERE	NONE	Resolved	+	No
#5	SAE	AFTER APH. 12M	SEPSIS	SEVERE	NONE	Resolved	+	No
#6	AE	AFTER APH. 12M	MUSCLE PAIN	MODERATE	NONE	Resolved	–	No
#7	AE	BEFORE APH.2	NAUSEA	MILD	NONE	Resolved	–	No
#8	AE	BEFORE APH.2	BLOATING	MILD	NONE	Resolved	-	No
#9	AE	BEFORE APH.2	HEADACHE	MILD	NONE	Resolved	-	No
#10	AE	BEFORE APH.5	BIATERAL LOWER EXTREMITY EDEMA	MILD	NONE	Not Resolved	–	No
#11	AE	APHER ESIS5	NAUSEA	MILD	NONE	Resolved	-	No
#12	AE	APHER ESIS5	VOMITTING	MILD	NONE	Resolved	-	No
#13	AE	APHER ESIS5	HEADACHE	MILD	NONE	Resolved	-	No
#14	AE	BEFORE APH.8	NAUSEA	MILD	NONE	Resolved	-	No
#15	AE	BEFORE APH.8	ABDOMINAL PAIN	MILD	NONE	Resolved	-	No
#16	AE	BEFORE APH.9	HEADACHE	MILD	NONE	Resolved	-	No
#17	AE	APHERE SIS9	NAUSEA	MILD	NONE	Resolved	-	No

The FDA agrees with the attribution of all events. In the previous report, the sponsor had reported one event (# 10) of embolism and thrombosis of the vena cava. That was eventually determined to be related to an infected central venous catheter and therefore, not device related. Similarly, another event reported in the previous report (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 Liposorber 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. Other events listed in the table do not raise any new safety concerns.

The firm reported one event of arm thrombus in a pediatric patient. Through email communication, the sponsor provided additional information about this event. It that was determined to be related to a peripheral IV catheter that thrombosed due to underlying nephrotic syndrome related hypercoagulability. FDA agrees with this attribution. Other events listed in the table do not raise any new safety concern.

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), eight of fifteen (53%) of subjects had achieved either partial or complete remission one month after the last device therapy. However, 7/9 (78%) and 4/5 (80%) 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 (93%) 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 one acute kidney injury was possibly related.

The FDA reviewed adverse event data in adults with FSGS treated with the Liposorber device system. One adult patient was noted to have an embolus/thrombus of the vena cava. Through email exchanges, the sponsor provided additional information about this event stating that the sponsor and the primary investigator determined this event to be not related to the treatment since the patient had a tunneled hemodialysis line removed for tunnel infection with catheter tip cultures growing methicillin sensitive Staphylococcus epidermidis. Therefore, the cause of the embolus/thrombus of the vena cava in this patient was determined to be catheter related (not device related). The FDA review team agrees with this assessment and believes this event may have been due to the presence of a central venous catheter (CVC), which is required for the device therapy. If the central venous catheter was in the superior vena cava and was infected, the development of an embolus/thrombus in the vena cava could have been catheter related. Additionally, hypercoagulability is not listed as an adverse event for the Liposorber 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 reviewed adverse event data in pediatrics with FSGS treated with the Liposorber device system. In this reporting period, the sponsor reported one event of right arm thrombus in a pediatric patient. This event has been determined by the sponsor and the principal investigator to be not related to the treatment. Through email exchanges, the sponsor provided additional

information about this event stating that the patient was at high risk for thrombosis due to nephrotic syndrome and eventually had a thrombus in the peripheral IV line. This reviewer agrees with the above assessment. The other events occurring in pediatrics do not raise any new safety concerns.

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 November 29, 2024 including all publications written in English between December 8, 2023 to November 29, 2024 in PubMed 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: 0 report
4. Focal Segmental Glomerulosclerosis, Low-Density Lipoprotein (LDL)-Apheresis: 1 report
5. Apheresis, Child, Focal Segmental Glomerulosclerosis: 2 reports One additional article provided by the sponsor was also considered.

After reading the titles, abstracts, and full-texts, 2 articles were selected.

Summaries of the selected articles are included below.

Dharnidharka VR et al: Clinical characteristics and favorable treatment responses of recurrent focal segmental glomerulosclerosis (FSGS) or steroid-resistant nephrotic syndrome (SRNS) in children after kidney transplantation. Pediatric Nephrol. 2024 Jul 13. PMID: 39001911.

FDA Comment: In this report, amongst other things, a comparison of various treatment options was made for children with primary FSGS/SRNS who received a kidney transplant and had a recurrence of the disease. The authors note that, in addition to other therapies, the chances of complete/partial remission were significantly higher with LDL-apheresis (LDL-A) sessions and LDL-apheresis was identified as one of the only treatments that were associated with complete remission for such patients, also suggesting that there could be a role of performing early LDL-apheresis in such cases. The review did not provide a discussion of the risks of LDL-A.

Gianos E et al. Lipoprotein Apheresis (LA): Utility, Outcomes, and Implementation in Clinical Practice: A Scientific Statement From the American Heart Association. Arterioscler Thromb Vasc Biol. 2024 Oct 7. PMID: 39370995.

FDA Comment: In this scientific statement provided by the American Heart Association (AHA), they "review the history of LA, mechanisms of action, cardiovascular and renal outcomes data, indications, and options for treatment" of hypercholesterolemia, especially in high-risk patients with persistent hypercholesterolemia. This statement is focused towards cardiological outcomes of LA with very limited renal outcome discussion. Additionally, this statement does 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 12/01/2023-11/25/2024, there were no MDR reports.

VII. SUMMARY

FDA recommends:

Continued surveillance and will report the following to the PAC in 2026:

- Annual distribution number
- PAS follow-up results
- Literature review
    MDR/MAUDE review