FDA Executive Summary

Prepared for the
April 8, 2019 meeting of 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 postmarket experience with the use of the Liposorber® LA-15 System from Kaneka in pediatric patients for the treatment of nephrotic syndrome associated with primary focal segmental glomerulosclerosis 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 familial hypercholesterolemia (FH) (depending on the patient's LDL-C levels), in the 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 focal segmental glomerulosclerosis (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.

V. POSTMARKET DATA: ANNUAL DISTRIBUTION NUMBER

Section 520(m)(6)(A)(ii) of The Food, Drug, and Cosmetic Act (FD&C) 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 regmen includes 12 treatments/patient, the total ADN is 96,000.

Section 613(b) of the 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 Federal Food, Drug, and Cosmetic Act (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 Federal Food, Drug, and Cosmetic Act (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 2018 in the United States

Table 1. Annual Distribution Number-Calendar Year Jan-Dec 2018

Device	Total Sales
MA-03 Apheresis Machine	1 Machine
Liposorber® LA-15 LDL Adsorption Column	378 pcs
Sulflux® KP-05 Plasma Separator	372 pcs
NK-M3R (U) Tubing System for Plasmapheresis	390 sets

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 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 will be 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, includingeGFR 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:

At the time of the four year interim report (H120005/R013), received at FDA on October 09, 2018, the sponsor reported that Institutional Review Board (IRB) approval had been obtained for seven clinical sites, and, fourteen subjects had been enrolled (Table 2). As of January 2019, the sponsor reported that no additional subjects had been enrolled since the prior year's annual

report. According to the most recently approved study timeline, 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: Patient Enrollment and Study Status

Interim Report	Date Received	Sites Enrolled	Patients 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.

Although the slow enrollment was expected, as this is a rare condition, especially in pediatric patients, enrollment is lower than anticipated based on the low prevalence of the intended use population, the weight restriction for study inclusion, and other potential factors. Due to the study's slow enrollment, the study status was determined to be "Progress Inadequate." 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. One barrier was attenuated by lowering the permissible weight at enrollmnent from 21 kg to 18 kg. FDA issued a deficiency to request more information about the barriers to enrollment and ascertain a plan from the sponsor how they could improve enrollment. The sponsor reports that the 3-4 hour treatment time is another barrier to enrollment, as well as the time associated with IRB application and approval. The sponsor has attempted to target major medical centers with high volume prescribers, and expects to enroll three additional sites.

Distribution of subjects' demographics is presented in Table 3 below.

Table 3. Demographics of Subjects (n=14)

	n	%
Age (years)		
6 - 8	5	35.7
9 - 11	3	21.4
12 - 14	4	28.6
15 - 17	0	0
18 - 20	2	14.3
Sex		
Male	7	50
Female	7	50
Race/ethnicity		
Caucasian	8	57.1
African American	2	14.3
Hispanic/Latino	2	14.3
Unknown	2	14.3

Source: Constructed based on data from H120005/R010

Follow-up is ongoing, its status per study visit is shown in Table 4 below. Of the 14 subjects enrolled in the study, there have been seven withdrawals, including two in the current reporting period. The reasons for withdrawal are listed in Table 5 below. Two subjects are in active follow-up. Since study inception, there have been two protocol deviations (two patients 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 one subject who withdrew and then underwent a second round of treatment.

Table 4. Subject Follow-up per Study Visit

Study Visit	Completed	Withdrawn	Active	Total
~9 weeks Apheresis Procedures	11[a, b]	1	0	12
1-month	9[b]	3	0	12
3-month	7[b]	1	0	8
6-month	6[b]	1	0	7
12-month	4[b]	1	1	6
24-month	2	0	1[b]	3

[a] One subject did not start treatment due to thyroid disease; [b] Including two protocol deviations;
Source: Constructed based on data from H120005/R010

Table 5. Reasons for Withdrawal/Exclusion

Subject/Patient ID	Status	Reason
(b	Withdrew after 6M	Subject moved to another hospital and had further treatment off the study.
(b	Withdrew after 3M	Subject relapsed and had another treatment series off the study.
(b	Withdrew after treatment	UnSubject dropped out and was lost to follow-up.

(b)	Exclusion (treatment not started)	Subject was revealed to have thyroid disease after enrollment (Medical Exclusion Criteria #8)
(b)	Exclusion (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.
(b)	Withdrew after 12M	Unknown
(b)	Exclusion (continuing active follow-up)	The reported Up/c of ACH004 at baseline was 0.08, which indicated that the patient achieved complete remission before treatment and was considered be inappropriate for treatment.
(b)	Withdrew after 1M (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.
(b)	Withdrew after 1M (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.
(b)	Withdrew after 1M	Unknown

Source: Constructed based on data from H120005/R013

Interim Results

Probable Benefit

Primary probable benefit endpoint: percentage of patients who show complete or partial remission at 1 month after the final apheresis treatment
Secondary probable benefit endpoint: percentage of patients who show complete or partial remission at 3, 6, 12, and 24 months after the final apheresis treatment

At one month follow-up, three of seven subjects in whom Urine Protein/Creatinine Ratio Up/c) data was available had achieved partial remission. One subject had missing Up/c data at one month and therefore remission status was uncertain; this patient had nephrotic syndrome 3 months after the final Liposorber treatment. Four of six patients who were followed for three or six months had complete or partial remission at three or six month follow-up, and the other two had no remission (nephrotic syndrome persisting). At 12-month follow-up, two patients had complete remission and the third had nephrotic syndrome. The subject outcomes and current status are shown in Table 6 below. Subjects (b) and (b) are not included in the table bacause they withdrew after the last treatment without follow-up labs (b) or were ineligible for inclusion (b). Subjects (b) (baseline glomerular filtration rate 39.8 ml/min) and (b) (urine protein-to-creatinine ratio not consistent with nephrotic syndrome) are not included in the table because they did not meet study inclusion criteria and therefore are considered protocol deviations and excluded from the probable benefit results; however these subjects continued follow-up visits. Subject (b) met criteria for nephrotic syndrome at 1, 3, 6, and 12-month follow-up. Subject (b) met criteria for complete remission at 1, 3, 6, and 12-month follow-up.

Table 6. Remission Status Based on Urine Protein/Creatinine (Up/c) Ratio

Patient ID	1-month	3-month	6-month	12-month	24-month	Status
(b	Partial	Partial	Partial			Withdrew after 6 mo visit
(b		NS				Withdrew after 3 mo visit
(b	NS	Partial	Complete	Complete	Complete	Completed study
(b	Partial	Complete	Partial	Complete	Complete	Completed study
(b	NS	NS	NS	NS		Withdrew after 12 mo visit
(b)	NS					Withdrew after 1 mo visit
(b)	NS					Withdrew after 1 mo visit
(b	Partial	Partial	Partial	Complete		Active
(b	Not done	NS	NS			Active

NS=Nephrotic Syndrome; [a] Gray shading indicates that data will not be collected (i.e., missing data or subject withdrew), and absence of shading indicates that data were or will be collected; [b] No subjects had reached 24 mo visit window.

Source: Constructed from Table 3 of H120005/R013

Safety

Primary safety endpoint: device-related and procedure-related serious adverse events (SAEs): The most common or serious adverse events with the Liposorber LA-15 system are listed in table 7 below:

Table 7. 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 five year report, sixty-seven adverse events have been reported. Table 8 shows the most serious events that have been observed. The events include nausea/vomiting/diarrhea/abdominal pain/ache, fever/infection, upper respiratory symptoms, headache, lightheadedness/fainting, hypotension, anemia, malaise, and weakness. The sponsor posits and the agency agrees that these events are most likely related to the patients' underlying conditions and/or the requirement for a central venous catheter for vascular access.

Table 8. Summary Table of Major Adverse Events

Adverse Event Type	Number of Events	Relationship to Device
Gastrointestinal (Nausea/ Vomiting/ Diarrhea/Ache)	9	None
Fever/Infection	12	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
Pneumonia	1	None
Bacteremia	1	None
Anemia	1	None

Source: Based on data from H120005/R013

Secondary probable benefit endpoint: laboratory values, including eGFR

Laboratory values including estimated glomerular filtration rate (eGFR) by study visit are shown in Table 9 below. The table shows that among the 9 subjects who completed full device treatment and had at least one post-treatment visit with laboratory results, eGFR was stable or increased in all but one subject. All but two subjects displayed either stabilization or decline 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 9. Renal Function (measured by estimated glomerular filtration rate) and other laboratory values by study visit

Table 9. Trends in Laboratory Values

Subject	Baseline eGFR	Last eGFR	Trend in eGFR	Baseline U p/c	Last U p/c	Trend in U p/c
(b [redacted]	62	84	Increase	44.3	17.5	Decrease
(b [redacted]	89	79	Stable	8.1	6.3	Stable
(b [redacted]	85	100	Increase	6.3	0.4	Decrease
(b [redacted]	171	132	Stable	1.9	0.2	Decrease
(b [redacted]	60	34	Decrease	1.8	3.8	Increase
(b [redacted]	85	130	Increase	4.8	3.7	Stable
(b [redacted]	153	161	Stable	4.1	4.6	Stable
(b [redacted]	78	69	Stable	1.1	0.7	Stable
(b [redacted]	60	83	Increase	5.4	8.3	Increase

Source: Constructed from Table 2 of H120005/R013Source: Constructed from Table 2 of H120005/R010/A001

FDA Conclusions About Probable Benefit and Safety:

Conclusions are very limited due to the small number of subjects and a limited period of follow-up in many patients. For probable benefit, at the one month follow-up period, three of seven subjects (43%) had achieved partial 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 majority (7/10; 70%) of patients, albeit a brief follow-up period for some patients. The rates and severity of adverse events were relatively low considering the underlying patient risk profiles (chronic kidney disease with nephrotic syndrome) and the known risks associated with any extracorporeal therapy. The agency asked the sponsor to provide explanation regarding the relatedness of the observed adverse events to the device. The sponsor replied with information in the adverse events table, shown in the column "Rationale for determination". The review team concurred with the sponsor that the adverse events were unrelated to the device. Enrollment has been slow due to the low prevalence of FSGS in the pediatric population; therefore, the study status has been changed to "Progress Inadequate." 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

The sponsor did not include a literature review for this reporting period. FDA conducted a literature search on February 15, 2019 in PubMed without any filters by using Kaneka, Liposorber, and Drug-resistant Pediatric Primary Focal Segmental Glomerulosclerosis. No articles were found published during 2018.

Overview of MDR Database

Strengths and Limitations of MDR Data

Each year, the FDA receives several hundred thousand medical device reports (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 potential 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.

MDRs Associated with the Liposorber® LA-15 System

The MDR Database was searched on January 3, 2019 utilizing the following search criteria:

- Product codes MMY (Lipoprotein, Low Density, Removal) and PBN (Apheresis for Focal Glomerulosclerosis in Pediatric Patients).

- A date range between January 1, 2018 and December 31, 2018

The search resulted in four (4) MDRs (3002808904-2018-00013, 3002808904-2018-00014, 3002808904-2018-00015 and 3002808904-2017-00002) for the Liposorber® LA-15 system. These MDRs do not involve pediatric patients and, therefore, may not be relevant to the Liposorber® LA-15 system use in pediactrics. Summary level information is provided only for completeness. No additional MDRs were submitted by the manufacturer during this time.

Adult Female Pregnant Pre-Eclampsia MDRs (n=3), Serious Injury

These reports (MDR 3002808904-2018-000139614654-2017-00006, 3002808904-2018-00014, and 3002808904-2018-00015), involved hypotensive events which occurred during apheresis treatment with the Liposorber® LA-15 System. These patients were part of a clinical study outside of the US. All females recovered after medical intervention and subsequently delivered via cescarian section. The current device labeling is adequate as hypotension is a known complication of the device, and in the device labeling.

Adult Male MDR (n=1), Serious Injury

One MDR was submitted from Japan, involving an adult male patient receiving hemodialysis for end stage renal disease who was also receiving therapy with the Liposorber® LA-15 to treat artericlerostic obliterans (ASO). The patient problems reported included hypotension and loss of consciousness after beginning treatment, resulting in an inmeasurable blood pressure. He regained consciousness after intensive medical intervention. Event date for this injury report (MDR 3002808904-2017-00002) was August 1, 2018. Since hypotension is included in the labeling, and may have occurred due to the Liposorber device but also due to the application of two extracoporeal therapies during a certain time frame in a single patient (risk factor for hemodynamic compromise), no labeling changes are required.

VII. SUMMARY

FDA recommends:

1. Continued surveillance and will report the following to the PAC in 2020:

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