FDA Executive Summary

Prepared for the
March 23, 2018 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 an update to the Pediatric Advisory Committee on postmarket data and 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 Food and Drug Administration (FDA) seeks feedback on potential safety concerns associated with the use of this device in children. This executive summary will include postmarket follow-up of the premarket clinical study, the peer-reviewed literature associated with the device, and postmarket medical device reporting (MDR) for adverse events.

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 system that includes disposable components and a control/monitor unit.

The Liposorber LA-15 System 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.

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 AND 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 2017 in the United States.

Table 1. Annual Distribution Number-Calendar Year Jan-Dec 2017

Device	Total Sales
MA-03 Apheresis Machine	2 Machines
Liposorber® LA-15 LDL Adsorption Column	336 pcs
Sulflux® KP-05 Plasma Separator	354 pcs
NK-M3R (U) Tubing System for Plasmapheresis	354 sets

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

PAS Study Design

The Liposorber HDE (H120005) was approved on October 10, 2013, with the following study design:

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 a GER 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, 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.

PAS Study Status

At the time of the four year interim report (H120005/R010), received at FDA on October 13, 2017, and the response to deficiencies (H120005/R010/A001) received at FDA on January 12, 2018, the sponsor reports that IRB approval has been obtained for six clinical sites and fourteen subjects have been enrolled (Table 2). This represents an increase of five subjects in the past year. 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 below shows enrollment into the study to date. 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 and is seeking feedback from the the advisory committee about strategies to enhance enrollment into the study.. 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 a plan from the sponsor how they plan to address the study status and 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. As of January 11, 2018, the sponsor reported that no additional subjects had been enrolled since the interim report received on October 13, 2017.

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 (R001)	7/8/14	0	0	Study Pending	
12-month (R002)	10/2/14	0	0	Progress Adequate	
18-month (R004)	4/6/15	3	0	Progress Adequate	
24-month (R005)	10/1/15	3	4	Progress Adequate	
36-month (R007)	10/4/16	3	9	Progress Inadequate	• Worked with sponsor to revise study timeline • Provided recommendations for enrollment strategies
39-month (R008)	12/28/16	4	9	Progress Adequate	
48-month (R010)	10/13/17	6	14	Progress Inadequate	• Deficiency letter issued to request plan from sponsor for

Interim Report	Date Received	Sites Enrolled	Patients Enrolled	Study Status	Actions Taken by FDA
					improving enrollment

Source: Constructed based on data from H120005/R001 through R010

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 status per study visit is shown in Table 4 below. Of the 14 subjects enrolled in the study, there have been five withdrawals. The reasons for withdrawal are listed in Table 5 below. There were two protocol deviations (should have been excluded from study due to not meeting inclusion criteria). Six subjects are in active follow-up. The two subjects who were protocol deviations are still undergoing follow-up visits, as well as the two subjects 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]	0	2	14
1-month	10[b]	1	2	13
3-month	8[b]	2	2	12
6-month	6[b]	1	3	10
12-month	5[b]	1	3	9
24-month	0[c]	0	8[b]	8

[a] One subject did not start treatment due to thyroid disease; [b] Including two protocol deviations; [c] None reached yet.

Source: Constructed based on data from H120005/R010

Table 5. Reasons for Withdrawal/Exclusion

Subject	Status	Reason
1	Withdrew after 6M	Subject moved to another hospital and had further treatment off the study.
2	Withdrew after 3M	Subject relapsed and had another treatment series off the study.
4	Withdrew after treatment	Subject dropped out and was lost to follow-up.
5	Exclusion (treatment not started)	Subject was revealed to have thyroid disease after enrollment (Medical Exclusion Criteria #8)
6	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.
9	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.
10	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.
11	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.

Source: Constructed based on data from H120005/R010/A001

Interim Results

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 P/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 #6 (baseline glomerular filtration rate 39.8 ml/min) and #9 (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 #6 met criteria for nephrotic syndrome at 1, 3, 6, and 12-month follow-up. Subject #9 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[a]	3-month	6-month	12-month	24-month[b]	Status
(b) (6)	Partial	Partial	Partial			Withdrew after 6mo visit
		NS				Withdrew after 3mo visit
	NS	Partial	Complete	Complete		Active
	Partial	Complete	Partial	Complete		Active
	NS	NS	NS	NS		Active
	NS					Withdrew after 1mo visit
	NS					Withdrew after 1mo visit
	Partial	Partial				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/R010

*Primary safety endpoint: device-related and procedure-related serious adverse events (SAEs):*Sixty-one adverse events have been reported (Table 7). The sponsor reported that most of the events were not related to the treatment. The events that were "possibly related" to treatment are shown in Table 8 below and include nausea/vomiting/diarrhea/abdominal pain/ache, fever/infection, upper respirotry symptoms, headache(, lightheadedness/fainting, hypotension, anemia, malaise, and weakness. The FDA sought further information about the AEs to better determine if the events may have been related to the device therapy. The sponsor provided more information which helped the agency assess the relatedness of the events to the device., The agency concurred with the sponsor that these AEs were more likely related to the patients' underlying conditions and/or the requirement for a central venous catheter for vascular access. Events #29-#61 occurred after treatment, during the follow-up period.

Table 7. Adverse Events (AE) and Serious Adverse Events (SAE) Reported by Sponsor

	AE/SAE	Patient ID	Report Stage	Date of occurrence	Description of AEs/SAEs	Severity	Hos-pitali-zation	Relationship to treatment (Attending Physician)	Relationship to treatment (Kaneka)	Ration-ale
(b) (6)	AE	(b) (6)	2 year	2015/4/ 6	Leg cramps	Mild	-	Not related	Not related	(1)
	SAE		2 year	2015/4/ 7	Bacteremia	Mild	+	Not related	Not related	(1)
	AE		2 year	2015/4/26	Diarrhea	Mild	-	Not related	Not related	(1)
	SAE		2 year	2015/5/ 6	Left mandibular pain, R/O infection	Mild	+	Not related	Not related	(1)
	SAE		2 year	2015/6/ 4	Cellulitis of left hip area	Mild	-	Not related	Not related	(1)
	AE		3 year	2015/9/9	Fever 103 , R/O line infection. – culture, + viral illness	Moderate	-	Not related	Not related	(1)
	SAE		3 year	2016/1/22	Fever max 100.7 , Diarrhea, Abdominal pain, Vomiting	Moderate	+	Not related	Not related	(1)
	AE		4 year	1): 2016/2/2 2) 3): 2017/2/29	1) Anemia 2) Transient decrease in serum protein and albumin levels 3) Headcahe, Hypotension (97/56mmHg)	Mild	-	Not related	Possibly related	(2)
	AE		4 year	2017/3/31	Stomachache	Mild	-	Not related	Possibly related	(2)
	AE		4 year	2017/4/1	Headache	Mild	-	Not related	Possibly related	(2)
	AE		4 year	2017/4/5	Headache, Leg cramp	Mild	-	Not related	Possibly related	(2)
	AE		4 year	2017/4/6	Nausea	Mild	-	Not related	Possibly related	(2)
	AE		4 year	2017/5/7	Cough, Congestion, Stuffy nose, and Runny nose	Mild	-	Not related	Not related	(3)
	AE		4 year	2017/5/7	Cough	Mild	-	Not related	Not related	(3)
	AE		4 year	2017/4/18	Headache	Mild	-	Not related	Possibly related	(2)

(b) (6)		(b) (6)								
	AE		4 year	1): 5/1/2017 2): 5/2/2017	1) Malaise 2) Headache	Mild	-	Not related	Possibly related	(2)
	AE		4 year	2017/5/4	Headache	Mild	-	Not related	Possibly related	(2)
	AE		4 year	2017/5/27	Nausea, Vomiting	Severe	-	Not related	Possibly related	(2)
	SA		4 year	2017/5/27 at 20:45	Feels Rreally Weak, Diarrhea, Vomiting (2 days), Abdominal pain, and Nausea	Severe	+	Not related	Possibly related	(2)
	AE		4 year	2017/8/15	Nausea	Mild	-	Not related	Possibly related	(2)
	AE		4 year	2017/8/16	Headache	Mild	-	Not related	Possibly related	(2)

(b) (6)	**AE/SAE**	**Patient ID**	**Date of occurrence**	**Treatment visit**	**Description of AEs/SAEs**	**Severity**	**Hos-pitali-zation**	**Relationship to treatment (Attending Physician)**	**Relationship to treatmen (Kaneka)**	**Ration -ale**
	AE	(b) (6)	2016/1/12	V2	fainting/lightheadedness	Mild	-	Not related	Possibly related	(2)
	AE		2016/4/19	V1	lightheadness	Mild	-	Not related	Possibly related	(2)
	AE		2016/6/2	V11	lightheadness/leg cramps	Mild	-	Not related	Possibly related	(2)
	AE		2016/6/21	V1	sinus pressure; hypotension	Mild; Moderate	-	Not related	Possibly related	(2)
	AE		2016/7/24	V9	nausea and vomiting	Mild	-	Not related	Possibly related	(2)
	AE		2017/9/12	V8	infection	Mild	-	Not related	Possibly related	(2)
	AE		2017/9/19	V9	nausia	Mild	-	Not related	Possibly related	(2)

	AE/SAE	**Patient ID**	**Date of occurrence**	**Treatment visit**	**Description of AEs/SAEs**	**Severity**	**Hos-pitali-zation**	**Relationship to treatment (CRF)**	**Relationship to treatmen (Kaneka)**	**Ration -ale**
(b) (6)	AE	(b) (6)	3/7/'16	FUV_3M	Elective Surgery	Mild	-	Not related	Not related	(4)
	AE		3/7/'16		Admission Post-op	Mild	-	Not related	Not related	(4)
	AE		5/2/'16	FUV_6M	Elective Surgery	Mild	-	Not related	Not related	(4)
	AE		5/2/'16		Elective Surgery	Mild	-	Not related	Not related	(4)
	AE		12/15/'16	FUV_12M	Itching	Mild	-	Not related	Not related	(4)
	AE		11/21/'16		Nausea	Moderate	-	Not related	Not related	(4)
	AE		12/15/'16		Dry Heaving	Moderate	-	Not related	Not related	(4)
	AE		11/21/'16		Sneezing	Mild	-	Not related	Not related	(4)
	AE		11/21/'16		Congestion (Nasal)	Mild	-	Not related	Not related	(4)
	AE		11/21/'16		Sore Throat	Mild	-	Not related	Not related	(4)
	AE		11/21/'16		Coughing	Mild	-	Not related	Not related	(4)
	AE		11/21/'16		Decreased Appetite	Moderate	-	Not related	Not related	(4)
	AE		11/22/'16		Bladder Pain	Mild	-	Not related	Not related	(4)
	AE		12/20/'16		Elbow Contusion	Mild	-	Not related	Not related	(4)
	AE		12/20/'16		Elbow Abrasion	Mild	-	Not related	Not related	(4)
	AE		5/10/'16		C. DifficileInfection	Moderate	-	Not related	Not related	(4)
	AE		1/27/'17	FUV_12M	Sore Throat	Mild	-	Not related	Not related	(4)

(b) (6)	AE	(b) (6)	1/27/'17		Fever	Mild	-	Not related	Not related	(4)
	AE		11/30'26	FUV_6M	Sore Throat	Mild	-	Not related	Not related	(4)
	AE		1/1/'17		Cough	Mild	-	Not related	Not related	(4)
	AE		1/1/'17		Sore Throat	Mild	-	Not related	Not related	(4)
	AE		1/1/'17		Rhinorrhea	Mild	-	Not related	Not related	(4)
	AE		2/21/'17	FUV_12M	Bilateral Leg Cramps	Moderate	-	Not related	Not related	(4)
	AE		5/26/'17		Cough	Mild	-	Not related	Not related	(4)
	AE		5/26/'17		Sore Throat	Mild	-	Not related	Not related	(4)
	AE		5/26/'17		Nasal Congestion	Mild	-	Not related	Not related	(4)
	AE		11/13/'16	FUV_3M	Abdominal Pressure	Mild	-	Not related	Not related	(4)
	AE		10/22/'15	FUV_1M	Proteinuria	Moderate	-	Not related	Not related	(4)
	AE		10/29/'15		Pneumonia	Mild	-	Not related	Not related	(4)
	AE		12/4/'15	FUV_3M	Rash	Mild	-	Not related	Not related	(4)
	AE		12/7/'16		Fever	Mild	-	Not related	Not related	(4)
	AE		6/13/'16	FUV_1M	Leg Pain	Mild	-	Not related	Not related	(4)
	AE		6/13/'16		Headache	Mild	-	Not related	Not related	(4)

Rationale:

1) **The DSMB agreed with the original evaluation "Not related".**
2) **The IFU and the Operator's Manual stated those AEs/SAEs may be associated with use fo the device.**
3) **Attending physician mentioned that the patient had upper respiratory tract infection at the time of treatment.**
4) **Kaneka consider that AEs/SAEs which occurred out of treatment period are basically not related to treatment and support the original evaluation.**

Source: Tables 5-7 from H120005/R010/A001

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	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
Pneumonia	1	None
Bacteremia	1	None
Anemia	1	None

Source: Based on data from H120005/R010/A001

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 and the trends in these lab values are displayed in table 10 below.

Table 9. Laboratory Values by Study Visit

Patient ID	Parameter	Unit	Baseline	After final treatment	1M F/U	3M F/U	6M F/U	12M F/U	24M F/U	Notes
(b) (6)	Up/c*1	g/g·CRE	44 33	13 02	17 43	12 81	17 51			
	sCR*2	mg/dl	0 8	0 4	0 6	0 6	0 6	WD*4		Withdrawal after 6M F/U
	eGFR*3	ml/min/1 73 m2	62 2	125 4	83 6	83 0	83 9			
	LDL-C	mg/dl	60	71	269	344	498			
	Up/c*1	g/g·CRE	8 11	3 84	N/A	6 27				
	sCR*2	mg/dl	0 7	0 7	0 7	0 8	WD*4			Withdrawal after 3M F/U
	eGFR*3	ml/min/1 73 m2	89 4	91 0	89 7	78 7				
	LDL-C	mg/dl	212	30	181	189				
	Up/c*1	g/g·CRE	6 33	<5 0	3 33	0 90	0 18	0 08		
	sCR*2	mg/dl	0 8	0 4	0 6	0 6	0 7	0 7		F/U
	eGFR*3	ml/min/1 73 m2	84 9	172 2	112 9	114 3	98 3	100 3		(12-month)
	LDL-C	mg/dl	345	23	96	70	78	45		
	Up/c*1	g/g·CRE	5 05							
	sCR*2	mg/dl	0 6							
	eGFR*3	ml/min/1 73 m2	95 8	WD*4						Withdrawal after treatments w/o F/U
	LDL-C	mg/dl	73							
	Up/c*1	g/g·CRE	8 16							
	sCR*2	mg/dl	0 7							
	eGFR*3	ml/min/1 73 m2	72 9	WD*4						Not started due to thyroid disease
	LDL-C	mg/dl	N/A							
	Up/c*1	g/g·CRE	1 05	0 68	3 99	8 18	3 51	4 54		
	sCR*2	mg/dl	1 9	1 8	1 9	2 7	2 5	3 8		F/U
	eGFR*3	ml/min/1 73 m2	39 8	42 0	39 6	27 9	30 2	19 8		(12-month)
	LDL-C	mg/dl	165	37	150	316	194	249		
	Up/c*1	g/g·CRE	1 98	0 71	0 39	0 10	0 42	0 17		
	sCR*2	mg/dl	0 3	0 3	0 4	0 4	0 4	0 4		F/U
	eGFR*3	ml/min/1 73 m2	170 7	170 3	129 1	129 8	130 1	132 2		(12-month)
	LDL-C	mg/dl	126	26	98	91	115	179		
	Up/c*1	g/g·CRE	1 81	3 48	2 67	2 11	4 01	3 78		
	sCR*2	mg/dl	1 2	1 2	1 4	1 2	1 4	2 2		F/U
	eGFR*3	ml/min/1 73 m2	60 0	60 0	51 9	60 9	52 5	33 9		(12-month)
	LDL-C	mg/dl	96	21	98	86	138	143		
	Up/c*1	g/g·CRE	0 08	0 07	0 16	0 08	0 07	0 05		
	sCR*2	mg/dl	1 2	0 4	0 6	0 5	0 5	0 5		Excluded from the
	eGFR*3	ml/min/1 73 m2	158 5	158 7	106 0	127 2	128 0	127 2		study
	LDL-C	mg/dl	103	21	110	108	121	120		
	Up/c*1	g/g·CRE	4 78	3 01	3 66					
	sCR*2	mg/dl	2 1	0 5	0 4					Withdrawal after F/U
	eGFR*3	ml/min/1 73 m3	84 7	103 8	129 8	WD*4				(1-month)
	LDL-C	mg/dl	N/A	4	81					
	Up/c*1	g/g·CRE	4 1	5 21	4 58					
	sCR*2	mg/dl	0 3	0 3	0 3					Withdrawal after F/U
	eGFR*3	ml/min/1 73 m2	153 0	159 1	160 8	WD*4				(1-month)
	LDL-C	mg/dl	N/A	7	110					
	Up/c*1	g/g·CRE	1 09	1 66	1 49	0 70				
	sCR*2	mg/dl	0 8	1 0	1 0	0 9				F/U
	eGFR*3	ml/min/1 73 m2	78 0	13	65 3	69 3				(3-month)
	LDL-C	mg/dl	44 0	13 0	100 0	78 0				
	Up/c*1	g/g·CRE	2 98							
	sCR*2	mg/dl	0 5							under treatment
	eGFR*3	ml/min/1 73 m2	48							
	LDL-C	mg/dl	48							
	Up/c*1	g/g·CRE	4 28							
	sCR*2	mg/dl	0 3							under treatment
	eGFR*3	ml/min/1 73 m2	162 6							
	LDL-C	mg/dl	123							
	Up/c*1	g/g·CRE	[redacted]*5							
	sCR*2	mg/dl	0 7							under treatment
	eGFR*3	ml/min/1 73 m2	83 2							
	LDL-C	mg/dl	56							
	Up/c*1	g/g·CRE	5 42							
	sCR*2	mg/dl	0 9							under treatment
	eGFR*3	ml/min/1 73 m2	60 3							
	LDL-C	mg/dl	N/A							

Up/c*1: urine protein:creatinine ratio sCR*2: Serum Creatinine eGFR*3: estimated glomerular filtration rate WD*4: Withdrawal

Source: Table 2 in H120005/R010/A001. Note: Patients (b) (6) withdrew and then received a second round of treatment (each round of treatment is represented by a separate row).

Table 10. Trends in Laboratory Values

Subject	Baseline eGFR	Last eGFR	Trend in eGFR	Baseline Up/c	Last Up/c	Trend in Up/c
(b) (6)	62	84	Increase	44.3	17.5	Decrease
	89	79	Stable	8.1	6.3	Stable
	85	100	Increase	6.3	0.8	Decrease
	40	20	Decrease	1.1	4.5	Increase
	171	132	Stable	1.9	0.2	Decrease
	60	34	Decrease	1.8	3.8	Increase
	159	127	Stable	0.1	0.1	Stable
	85	130	Increase	4.9	3.7	Stable
	153	161	Stable	4.1	4.6	Stable
	78	70	Stable	1.1	0.7	Stable

[a]Subjects (b) did not meet inclusion/exclusion criteria.
Source: Constructed from Table 2 of H120005/R010/A001

FDA Conclusions About Probable Benefit and Safety Based on the PAS Results
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 sponsored 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.

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, 2018 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, 2017 and December 31, 2017

The search resulted in two (2) MDRs (9614654-2017-00006 and 3002808904-2017-00005) for the Liposorber® LA-15 system. In addition, MDR 9614654-2017-00008, also submitted by the manufacturer during this time, references the Liposorber LA-40S (not sold in the U.S.). The manufacturer submitted this report because the event occurred on a device similar to the Liposorber LA-15 system.

Pediatric MDR (n=1), Serious Injury

This report (MDR 3002808904-2017-00005), involved a 9-year-old female in whom the LDL-apheresis (LDL-A) with the Liposorber® LA-15 System was being used for treatment of "Focal Segmental Glomerular Sclerosis (FSGS) with steroid resistant nephrotic syndrome". A catheter for blood draws was placed in the right internal jugular vein to begin treatment. The patient developed a fever one day after the 9th LDL-apheresis treatment (LDL-A). All previous treatments were conducted without problems. The patient was admitted to the hospital and her white blood cell (WBC) count was noted as 34,200/ml and blood cultures were found to be positive for *Escherichia coli*, which is noted to have resolved after administration of antibiotics. The 12th and final treatment occurred without any problem and discharge was planned after catheter removal.

The manufacturer's narrative stated that the LDL-apheresis procedure was unlikely to have been the cause of the infection and they "strongly suspected" the tunneled catheter for blood access, which was placed for over 40 days when the event occurred, to be the likely cause. The attending physician commented "that the relationship between the LDL-apheresis and the reported event is possibly related." The MDR was filed since the manufacturer could not deny the relevance between the LDL-apheresis and the incident with certainty.

Indeterminant Age MDRs (n=1), Serious Injury

One MDR was submitted from Japan, involving a patient of unknown gender and age and the use of the Liposorber® LA-15. The patient problems reported included shock, hypotension, loss of consciousness, and dyspnea. No device problems were associated with this patient event.

This injury report (MDR 9614654-2017-00006) involved an unidentified patient with peripheral artery disease (PAD) and diabetes, who was also on hemodialysis. The first set of LDL-A sessions using the Liposorber® LA-15 system for PAD were uneventful. During the first LDL-A procedure of the second set of LDL-A sessions, 30 minutes after the start and with 500 ml of treated plasma, this patient went into anaphylactic shock with a decrease in BP to "70-80mmHg". The symptoms subsided after the patient was given "supplementation fluid and steroid". The event narrative notes that the patient was given Heparin for anticoagulation during the LDL-A and was administered "loperamide". This patient did not take any angiotensin converting enzyme (ACE) inhibitor. It was noted that "some parts of the hollow fibers of the plasma separator (Sulflux FP-08), appeared colored in purple instead of the usual white in the completion of plasma/blood return procedure after treatment".

The manufacturer's narrative stated that after confirmation of the color change, the plasma separator was sent to the manufacturer, Asahi-Kasei Medical, for their investigation. In the manufacturer narrative, the attending physician commented that the plasma separator "might have been attributable to the reported patient's reactions". The manufacturer also stated they could not exclude the possibility that the LDL-A procedure was relevant to an acute hypotensive reaction occurrence since the extracorporeal volume in the LDL-A is larger than that of hemodialysis.

On December 8, 2018, the Office of Surveillance and Biometrics (OSB) sent a letter requesting additional information related to the discoloration of the plasma separator and the timing of the last hemodialysis (HD) treatment to the LDL-A treatment in question.

As noted in last year's Pediatric Advisory Committee meeting, the use of combination treatment of HD and LDL-A on the same day could exacerbate hypovolemic shock syndrome, given that the extracorporeal volume of the LDL-A system is larger than that of the HD system and the patient has already lost a certain amount of circulating blood volume.

Note: An injury report (MDR 9614654-2017-00008) was also submitted by the manufacturer during this review period because the event occurred on a similar device. This report references a female patient with "familial hypercholesterolemia being treated with LDL-A using Liposorber® LA-40S (not currently sold in the US)" once a week. At a processed plasma volume (PPV) of 700 ml, the patient began to feel sick and her blood pressure (BP) dropped to 117/55 with a pulse of 96 bpm. She was administered a rapid infusion of saline and her BP recovered but her pulse remained the same. LDL-A treatment was resumed and at a PPV of 1,000 ml, the patient lost consciousness and her BP became "unmeasurable". She was then treated with oxygen and "saline infusion with steroid and vasopressor". She regained consciousness as her BP continued to elevate and was then transferred to another hospital for respiratory and heart evaluation when she complained of dyspnea after an attempt to discontinue the oxygen. The manufacturer narrative for this report goes on to mention that this patient had been taking a long time prescribed diuretic, and an angiotensin receptor blocker (ARB) was added to the regimen 19 days prior to the date of event. The attending physician suspected bradykinin-related shock.

FDA Conclusions About MDRs

As indicated in the device Instructions for use (IFU), the patient problems reported in these 3 MDRs (shock, hypotension, and dyspnea), are known inherent risks with the use of this device. Based on this year's manufacturer evaluations contained in the MDRs and the device's IFUs, and as noted in the presentation made at the 2017 PAC panel meeting, there are certain factors physicians continue to need to consider when treating with LDL-A including, but not limited to:

I. A strong consideration of all concomitant medications the patient is taking such as:
    a. Use of an angiotensin-converting enzyme (ACE) inhibitor, which will activate bradykinin (a substance that causes vasodilation and hypotension), or
    b. Use of other anti-hypertensive drugs which can exacerbate other causes of hypotension.

II. The combination treatment of HD and LDL-A on the same day could exacerbate hypovolemic shock syndrome, given that the extracorporeal volume of the LDL-A system is larger than the HD system and the patient has already lost a certain amount of circulating blood volume.

The number of MDRs submitted each year continues to be relatively small (i.e. ranging from 0-8 MDRs received per year) as noted in prior presentations to the PAC.

2018 Update to the Systematic Literature Review on the Use of the Liposorber LA-15 Device in the Pediatric Population

Purpose

In preparation for the FDA PAC 2018 spring meeting, a systematic literature review was conducted to provide an update addressing the following question: *What use of the Liposorber LA-15 system is reported in the literature for the pediatric population (≤21 years old)?* This is an update from the literature review presented at the Pediatric Advisory Committee (PAC) meeting on March 3, 2017.

Methods

On November 29, 2017, a search was conducted using the PubMed (Medline) and EMBASE databases with the following search strategies:

(Liposorber OR (LDL AND apheresis))

The search was limited to articles published between December 5, 2016 (last date of search included in the previous literature review presented in PAC 2017) and November 29, 2017 (see Figure 1).

Results

There were 79 records identified in PubMed, and 120 records identified in Embase.
All 199 records were excluded, for the following reasons:

- Duplicate (n=66)
- Non-clinical study (n=51)
- Conference abstract (n=21)
- Not relevant; i.e., no use of LDL apheresis treatment (n=18)
- No use of LA-15 system or device not specified (n=31)
- No pediatric patients ≤21 years old (n=12)

Therefore, there was no new literature identified by the search.

FDA Conclusions About Literature Review

A systematic literature review was presented to the Pediatric Advisory Committee (PAC) in 2015 (15 articles presented, from years 1995-2014). An update to the literature review was presented in 2016 (one conference abstract presented) and 2017 (n=0 articles presented). For this year's PAC meeting, similar methodology was employed to update the literature review and determine if new information was available. The date range of the search was December 5, 2016 (date of last search) to November 29, 2017.

The search did not result in any new literature that reported on the use of the device in the pediatric population, for any indication. Therefore, the literature review provided no new probable benefit or safety information.

VII. SUMMARY

FDA Conclusions

Safety

The safety profile of the device for treatment of pediatric patients with FSGS remains acceptable. While the reported adverse events (AEs) were generally mild-moderate and resolvable, FDA notes the challenges in determining if some events may be related to the patient's underlying condition and/or the presence of a central venous catheter versus related to the device system. To date, the types, rates and severity of AEs in the PAS period deemed to be attributable to the device are consistent with those provided in the labeling.

Probable Benefit

About 40% of the patients treated with the device achieve either a partial or complete remission, with significant reduction in urine protein. The majority of patients display a stabilization of renal function (GFR), albeit over a limited follow-up period in several patients. These two trends suggest that there is a cohort of patients that are displaying some response to the device therapy and are major predictors of kidney health in patients with FSGS.

FDA Recommendations

FDA recommends:

1) Continuation of the PAS trial
2) Continued surveillance and report of the following by the sponsor to the PAC in 2019:
    a) Annual distribution number
    b) PAS follow-up results
    c) Literature review
    d) MDR review