FDA Executive Summary

Prepared for the
April 12, 2016 meeting of the
FDA's Pediatric Advisory Committee

H120005
Liposorber® LA-15 System

TABLE OF CONTENTS

I. INTRODUCTION

In accordance with the Pediatric Medical Device Safety and Improvement Act this review provides a safety update based on the postmarket experience with the use of the Liposorber® LA-15 System 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.

The purpose of this review is to provide the Pediatric Advisory Committee with postmarket safety data, so the committee can advise the Food and Drug Administration (FDA) on potential safety concerns associated with the use of this device in children. This executive summary will include summaries of the premarket clinical study, 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 extracorporeal blood processing system that includes disposable components and a control/monitor unit.

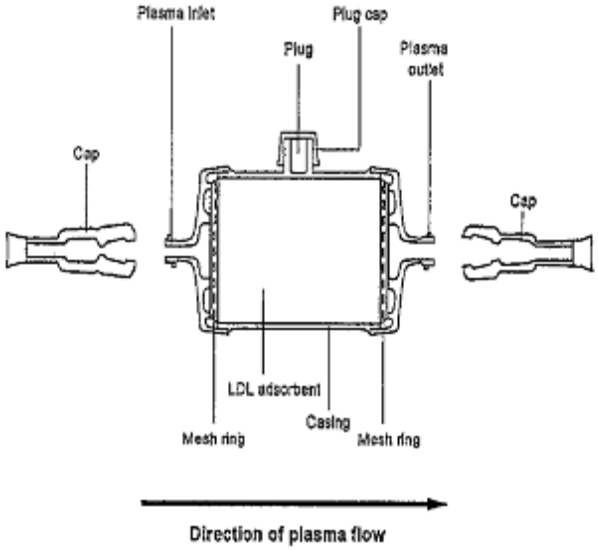
The components of the device are identical in material and design to the device currently approved via PMA P910018 (for subgroups of patients with familial hypercholesterolemia (FH)) and its supplements. The Liposorber® LA-15 System consists of four major components: the Sulflux KP-05 Plasma Separator, Liposorber® LA-15 Adsorption Columns, NK-M3R Tubing Set, and MA-03 Machine.

1. The Sulflux KP-05 Plasma Separator (approved on 6/27/2007 – Supplement 11) separates the plasma from whole blood. This component is comprised of porous hollow fibers made of polyethylene coated with an ethylene vinyl alcohol copolymer enclosed in a polycarbonate housing.

2. The Liposorber LA-15 Adsorption Columns (approved in original PMA 1996) (Table 1) are disposable. They adsorb apolipoprotein B-containing lipoproteins from a patient's

plasma as it passes through the columns. The casing of the columns is polycarbonate. Each column (they are used in pairs for a treatment) contains a microporous hydrophilic gel (with particle size of 64 – 160 µm) composed of 150 ml dextran sulfate cellulose (DSC) beads soaked in 0.04-0.08% (w/v) sodium citrate/citric acid solution.

Figure 1 Schematic of Liposorber LA-15 Adsorption Column



3. The NK-M3R Tubing Set (approved on 3/31/2009 – Supplement 12 and 6/18/2010 – Supplement 13) set is designed specifically for the Liposorber LA-15 System. The tubing is comprised primarily of polyvinyl chloride, but also contains polycarbonate, polypropylene, polyethersulfone, polytetrafluoroethylene, polyester, acrylic resin, isoprene rubber, and polyolefin elastomer. It is composed of the following:

    - Blood withdrawal line
    - Regeneration line
    - Plasma line
    - Blood return line
    - A set of five (5) connection lines (for connection to solution bags)
    - Membrane filter.

4. The MA-03 Machine (approved 3/31/2009 – Supplement 12) is a computer-controlled unit that controls the entire apheresis procedure.

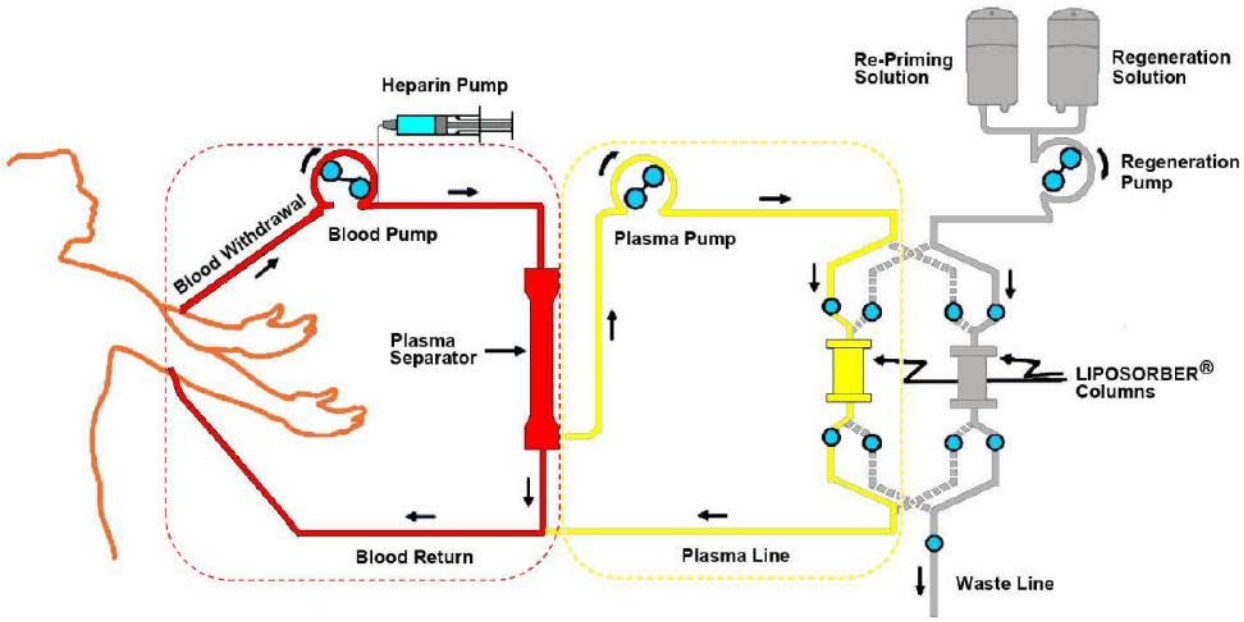
While the Liposorber® LA-15 System (P910018) is labeled for either weekly or every other week use when used to treat familial hypercholesterolemia (FH) (depending on the patient's LDL-C levels), in the HDE, the Liposorber (H120005) is indicated for up to 12 uses in 3 months for treatment of focal segmental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

Method of Operation:

The method of operation for the device for its pediatric indication is identical to the method of operation for the original indication (P910018), which is to treat hypercholesterolemia in certain high risk patient populations. The method of operation is described below, and Figure 2 is the schematic of this operation.

- Blood is withdrawn from the patient's arm via venous access.
- The blood is combined with heparin and pumped at a steady flow rate through the NK-M3R Tubing Set into the inlet port of the Sulflux KP-05 Plasma Separator to separate plasma from the cellular components of the blood.
- Plasma exits from the plasma outlet and the remaining blood, including red and white blood cells and platelets, exit from the blood outlet.
- The cell-free plasma is pumped into one of the two Liposorber LA-15 Adsorption Columns where apolipoprotein B-containing lipoproteins are adsorbed to the cellulose beads and removed from the plasma. The dextran sulfate cellulose beads have a strong affinity for apolipoprotein B-containing lipoproteins.
- Filtered plasma exits the column, passes through a membrane filter to ensure particles from the column do not enter the system, and is recombined with the cellular elements originally exiting the plasma separator.
- This recombined blood and plasma flow through a built-in blood warmer (part of the MA-03 Machine) and is returned to the patient via a second venous access.

Figure 2 Schematic of Liposorber Operation



Apheresis occurs on a continual basis even when a column has been exhausted, because the system regenerates one column while the other one is in use. When one column has completed an adsorption cycle, the computer-regulated machine automatically switches the plasma flow to the other column to continue adsorption. Simultaneously, the plasma remaining in the first column is returned to the patient. The first column is then regenerated using 5% Sodium Chloride Injection USP. Once the elution is completed and flushed through the waste lines to a waste bag, the column is reprimed and ready for the next cycle of adsorption, allowing continuous apheresis. No additional fluids are given to the patient during these column switch overs and only the filtered plasma is returned. The patient treatment takes about 2-3 hours and is performed at a medical facility.

The total extracorporeal volume of the circuit used with a Liposorber LA-15 Adsorption Column is 404 mL, which includes both plasma and whole blood together. The total volume of whole blood in the circuit is 160 mL. The total volume of additional plasma in the circuit is 244 mL. The 244 mL plasma portion of the circuit is drawn from and returned to the blood portion of the circuit. The entire system is primed with heparinized fluid before use, so the patient does not experience significant volume loss.

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. PREMARKET DATA: CLINICAL INVESTIGATION

Pediatric focal segmental glomerulosclerosis (FSGS) is a progressive and aggressive disease of the kidney that frequently leads to end stage renal disease (ESRD) in children. As the disease progresses, the filtering units of the kidney (called glomeruli) become sclerotic. In addition, other areas of the kidney (tubules, interstitium) develop inflammation and sclerosis, and some tubules, which carry fluid within the kidney and absorb nutrients, are permanently damaged and lost (atrophy). As a result, the ability of the kidneys to filter the blood properly is lost, resulting in poor renal function.

FSGS is a histologic (tissue-based) diagnosis that may have no identifiable cause, in which case it is called primary FSGS. FSGS may also be secondary to another disease (e.g., hypertension, vesicoureteral reflux). The primary form of FSGS is more common among children and young adults, while secondary FSGS is more common in older adults. Regardless, the initial insult is thought to involve damage to the glomerular epithelial cells (podocytes), leading to protein leak, capillary expansion, formation of synechiae, and mesangial matrix proliferation. The primary clinical symptom of FSGS is proteinuria. Other clinical symptoms are secondary to urine protein loss, and include hyperlipidemia, hypoalbuminemia, edema, and hypertension.

Treatment of primary FSGS is principally aimed at reduction of proteinuria. This can be accomplished with the use of drugs that suppress the immune system, including corticosteroids, calcineurin inhibitors, and cytotoxic agents. Other medications that target renin-angiotensin-aldosterone system blockade (e.g., angiotensin converting enzyme inhibitors (ACE) and/or

angiotensin receptor blockers (ARB)) decrease proteinuria and lower blood pressure which can slow the progression of proteinuric kidney diseases like FSGS. Nevertheless, spontaneous remission of primary FSGS is rare and the renal prognosis is poor, with FSGS patients frequently developing ESRD within 3-10 years. FSGS is much more likely to progress to ESRD than any other primary renal disease. For patients with primary FSGS who are refractory to standard treatments, there are generally no alternative options and progression to ESRD and lifelong renal replacement therapy (dialysis, transplant) is inevitable. Moreover, the lifespan of any child who develops ESRD is dramatically reduced, generally being 25-50 years.

The Liposorber® LA-15 System is for pediatric patients with primary FSGS only, since treatment of secondary FSGS primarily involves treatment of the underlying cause (e.g., hypertension).

The applicant did not conduct a prospective study regarding the proposed device for the intended populations. Instead, the applicant provided references for several studies of children with FSGS, either before or after renal transplant, who received therapy with the Liposorber® LA-15 System. Among the studies provided, all but two (one including patients with FSGS treated with the device prior to transplant, and one including patients with FSGS who received therapy after transplant) involved 1-2 patients. Only the larger studies were considered for assessment of the device for the intended populations.

Pre-transplant FSGS:

For the pre-transplant (FSGS) population, the applicant provided a published study (Hattori et al, 2003) which described the outcomes of eleven (11) children with steroid resistant primary FSGS who were treated unsuccessfully with conventional-dose cyclosporine therapy and showed persistent nephrotic range proteinuria. At the time of treatment with the Liposorber LA-15 System, none of the patients had received a renal transplant ("pre-transplant"). At the start of the 7^{th} apheresis treatment (average number of treatments: 11.5), prednisone was administered at a dose of 1mg/kg/d for 6 weeks, followed by a tapering schedule during subsequent months.

The effectiveness endpoint was the number of patients achieving remission of nephrotic syndrome. Other measures included renal function (i.e., glomerular filtration rate (GFR)), degree of proteinuria, cholesterol level and complications of therapy.

The criteria used to assess clinical response were:

- Remission of nephrotic syndrome (NS)
    - Complete remission: reduction in urinary protein (< 4 $mg/m^2/h$) for 3 consecutive days with normal serum albumin and cholesterol levels, and stable renal function
    - Partial remission: lower urinary protein levels but persistent non-nephrotic proteinuria (protein< 40 $mg/m^2/h$) with normal serum albumin
        - Renal Function (as GFR, in $ml/min/1.73m^2$)
        - Proteinuria ($g/m^2/day$).

Results:

Effectiveness:

- Achievement of remission (defined above) of nephrotic syndrome was observed in 7/11 patients (5 complete and 2 partial).

- Renal function (GFR) for the five (5) patients who achieved complete remission was normal during follow-up (median: 4.4 years, range: 4.0-11.1 years).

- Proteinuria declined in 7/11 patients (as evidenced by remission of nephrotic range proteinuria).

Safety:
Only one patient developed a complication (infection of the indwelling catheter used to receive the therapy).

Conclusion:
The authors suggest that combined LDL-apheresis and prednisone therapy can be a valuable therapeutic option for treating patients with steroid resistant FSGS. They also showed that patients with lower degrees of proteinuria and less advanced changes on renal biopsy prior to Liposorber treatment achieved higher rates of remission, lower levels of proteinuria and better preservation of GFR with therapy.

Post-transplant FSGS:
For the post-transplant FSGS population, the applicant provided a published study (Muso et al, 2007) of 41 patients with refractory FSGS. The study population included a sub-set of 7 patients (not defined but likely all adults) who developed recurrent FSGS after undergoing renal transplantation. The study was intended to evaluate the long-term outcome of LDL apheresis in patients with FSGS.

The criteria used to assess clinical response were:

- Change in lab values (e.g., serum protein, serum albumin, proteinuria) at 1 month after treatment and measured the number of patients achieving remission of nephrotic syndrome at 2 and 5 years after Liposorber treatment

- Remission of nephrotic syndrome (NS)

    - Complete remission

    - Type I incomplete remission: proteinuria negative or < 1.0 g/day and serum albumin > 3.0 g/dL

    - Type II incomplete remission: proteinuria < 3.5 g/day but serum albumin < 3.0 g/dL

Results:

Effectiveness:

- At 1 month after LDL apheresis total serum protein and albumin increased significantly and proteinuria was significantly decreased.

- Remission of nephrotic syndrome was observed in 18/29 patients followed at 2 years (62%).

- Remission of nephrotic syndrome was observed in 13/15 patients followed at 5 years (86%).

The seven post-transplant patients were included in the 41 patients analyzed at 1 month. The authors did not separate out the patients treated before and after transplant. The authors state that the exclusion of the post-transplant patient data did not impact the data trend or significance of the results, indicating that the post-transplant data were similar as a group to the pre-transplant patients in terms of increase in serum protein and albumin and decrease in proteinuria. The authors did not indicate the number of post-transplant patients included in the 2 and 5 year follow-up.

Safety:
The incidence of safety events was not reported.

Conclusion:
The authors conclude that early administration of LDL-apheresis after the onset of nephrotic syndrome associated with FSGS provides a good long-term outcome.

The studies listed above did not comprehensively assess safety of the device in either children or adults with FSGS. However, there was extensive experience and data of safety of the device system in children treated for familial hypercholesterolemia (FH). The agency posited that extrapolation of safety data in children with FH treated with the device system was reasonable since the risks for children with FH was similar to or greater than for children with FSGS. Therefore, an analysis was done to assess the safety of the device in children with FH treated with the Liposorber LA-15 system. Table 1 displays the incidence of various adverse events known to occur with the device system that occurred in children with FH treated with the Liposorber LA-15 system, as reported in two published manuscripts[1,2]:

Table 1 Incidence of Various Adverse Events Known to Occur in Children with FH Treated with the Liposorber LA-15 System

Adverse Event (Side Effect)	How Often This Happens in Children Treated with the Liposorber LA-15 System for Another Disease (High LDL-Cholesterol) Due to the System Itself	Harm to You
Death	Not reported to occur	Death

Adverse Event (Side Effect)	**How Often This Happens in Children Treated with the Liposorber LA-15 System for Another Disease (High LDL-Cholesterol) Due to the System Itself**	**Harm to You**
Cardiac (heart-related, including abnormal heart rhythm, slow heart rate, fast heart rate and heart attack)	Not reported to occur	Mild to serious
Thrombocytopenia (low count of platelets that help blood clot and prevent bleeding)	Not reported to occur	Mild to serious
Infection (local or widespread)	Occurred in 2 of 20 patients	Mild to serious
Hypersensitivity (allergic-type reaction to a part of the system)	Not reported to occur	Mild to serious
Nausea and vomiting (abdominal symptoms)	0.3-2.5% of treatments (1/333 to 1/40 treatments)	Mild
Low Vitamin E level (which can cause muscle weakness, nausea and vomiting)	Not reported to occur	Mild
Temporary decrease in blood protein level (including albumin which holds water in the blood vessels)	Not reported to occur	Mild to moderate
Hypotension (low blood pressure)	2.0-2.5% of treatments (1/50 to 1/40 treatments)	Mild to severe
Flushing/blotching of skin	Not reported to occur	Mild
Angina (chest pain)	0.2-0.3% of treatments (1/500 to 1/333 treatments)	Mild to moderate
Fainting/lightheadedness	Not reported to occur	Mild to moderate
Anemia (low blood count)	Not reported to occur	Mild to serious
Prolonged bleeding at intravenous or catheter site	Not reported to occur	Mild to moderate
Hemolysis (breaking up of red blood cells)	Not reported to occur	Mild to serious
System (machine or its parts) malfunction	Not reported to occur	Mild to serious

Adverse Event (Side Effect)	How Often This Happens in Children Treated with the Liposorber LA-15 System for Another Disease (High LDL-Cholesterol) Due to the System Itself	Harm to You
Vertigo (dizziness, unsteadiness)	0-0.3% of treatments (none to 1/333 treatments)	Mild to moderate
Diaphoresis (excess sweating)	Not reported to occur	Mild
Urticaria	Not reported to occur	Mild
Shivering	0-0.3% of treatments (none to 1/333 treatments)	Mild
Headache	0-0.5% of treatments (none to 1/200 treatments)	Mild

This safety data clearly shows that rates of adverse events known to occur with the Liposorber LA-15 system were very low. This data provided reasonable assurance that the risk of device-related adverse events to children with FSGS would be acceptable.

VI. POSTMARKET DATA: ANNUAL DISTRIBUTION NUMBER

The Food and Drug Administration Safety and Innovation Act (FDASIA) amended section 520(m) of the Federal Food, Drug, and Cosmetic Act (FD&C) and allowed 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). The ADN was defined to be the number of devices "reasonably needed to treat, diagnose, or cure a population of 4,000 individuals in the United States." FDA has interpreted that to imply that the calculation of the ADN should be 4,000 multiplied by the number of devices reasonably necessary to treat an individual. The approved ADN for the Liposorber® LA-15 System was 48,000 which takes into account that a single course of treatment requires 12 pairs of columns. Although the columns are sold as pairs, two a box, one box is considered a device and thus the ADN is calculated as 12 * 4,000 = 48,000. Table 2 shows the annual distribution number for 2015.

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. In 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 2 Annual Distribution Numbers

Calendar Year (Jan - Dec)	Total Sales
2015	(1) MA-03 Apheresis Machine: 3 machines (2) LIPOSORBER® LA-15 LDL Adsorption Column: 114 pcs (3) Sulflux® KP-05 Plasma Separator: 114 pcs (4) NK-M3R (U) Tubing System for Plasmapheresis: 114 sets

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

PAS Conditions of Approval:

The Liposorber HDE (H120005) was approved on October 10, 2013, with the following conditions of approval:

> *You have agreed to conduct a study as follows: 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 ESOS. 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 1-, 3-, 6-, 12- and 24-month follow-up office visits. 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 I -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 Protocol (H120005/S001/A001):

At the time of device approval there was agreement on a PAS outline and the full protocol was developed and approved postmarket, on April 25, 2014. A description of the study is provided below:

- *Study Objective and Design*: 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 primary objectives of this study are to evaluate the safety and probable benefit of the Liposorber LA-15 System in relieving nephrotic syndrome associated with refractory pediatric primary FSGS at 1 month after the final apheresis treatment.

- *Study Hypothesis*: No formal hypothesis will be tested in this study. However, to evaluate the primary probable benefit objective, the percent of patients with complete or partial remission (based on a first morning urine specimen at 1 month after the final apheresis procedure) will be determined and the 95% confidence interval will be constructed.

- *Study Population*: Pediatric patients with nephrotic syndrome associated with primary focal segmental glomerulosclerosis, when the standard treatment options, including corticosteroid and/or calcineurin inhibitors treatments, have been 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.

- *Sample Size*: A total of 35 patients will be included. The primary probable benefit endpoint will be assessed using a 95% confidence interval. The assumption for sample size calculation was that 50% of patients would achieve a 50% reduction in urine protein at 1 month. Optimal conservative medical therapy would be expected to be approximately 10% based on the collected data in Glomerular Disease Collaborative Network (University of North Carolina, Chapel Hill, NC). The reported clinical results in pediatric steroid-resistant FSGS treated with the Liposorber® LA-15 System suggest the incidence of favorable cases is at least 25%, implying that the probable benefit of the system is superior to that of ordinary medical therapies. With a performance goal of 25%, an expected rate of 50% of patients, a one-sided exact binomial test, and a type I error

rate of 0.025 (corresponding to a 95% one-sided confidence interval), 30 patients provides a power of 0.82.

- *Study Endpoints*:

  - The primary probable benefit endpoint is the percent of patients who show complete or partial remission at 1 month after the final apheresis treatment.
  - The primary safety endpoint is the rate of device-related and procedure-related serious adverse events (SAEs) occurring during the period in which the apheresis procedures are administered and up to at the 1-month follow-up visit.

  - Secondary endpoints are as follows:

    - Nephrotic condition (complete remission, partial remission, and nephrotic state) at 1, 3, 6, 12, and 24 months after the final apheresis treatment, including the percentage of patients who obtain complete or 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 AEs and SAEs occurring within 3, 6, 12, and 24 months after the final apheresis treatment

    - 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

- *Enrollment Plan and Follow-up Measures*: Preferred clinical sites will include physicians who have published in the field of treatment for pediatric FSGS. Since patients with FSGS are often referred to specialists at major medical centers, these larger centers are likely to be recruited due to referral patterns and physician specialists. Prior to enrollment in the study, the importance of keeping the study required scheduled visits will be stressed to both the patients and their guardians. If the patient or guardian feels that the required visits cannot reasonably be kept, the patient will not be enrolled in the study. In the event a patient does not arrive for treatment or scheduled follow-up, at least 3 attempts may be made to locate the patient and reschedule the visit.

- *Length of Follow-up*: Patients will be followed for 24 months after the final apheresis treatment.

- *Frequency of Follow-up Assessments*: Patients will undergo follow-up at 1, 3, 6, 12, and 24 months after the final apheresis treatment.

- *Statistical Plan*: Clinically-relevant baseline variables will be tabulated. Continuous variables will be reported as means and standard deviations unless otherwise noted. Categorical variables will be reported as percents. Covariate analysis may be performed to identify predictors of SAEs and/or remission. Covariate analysis will also be performed with transplant status (i.e., pre-transplant, post-transplant) as a variable to identify additional predictors of SAEs and/or remission. Survival analysis techniques such as Kaplan-Meier or Cox Proportional Hazards will be incorporated if censoring of data occurs. Missing data may be addressed using multiple imputation and complete-case analysis.

PAS Study Status:

At the time of the most current interim report (H120005/R005), received at FDA on October 1, 2015, the study has been initiated, and IRB approval was obtained in 3 clinical sites. A total of 4 subjects in 2 participating sites have been enrolled. Two of the 4 subjects completed the whole treatment course and the other two are under treatment as of September, 30, 2015. The study progress is consistent with the FDA approved timeline; therefore, the study progress is considered adequate.

The preliminary results so far are as follows:

- Substantial improvement in nephrotic symptoms was observed in the two subjects who completed the treatment course.

Table 3- Treatment status

Subject ID	Dates of Treatment		Up/c level				eGFR			
	1st	12th	BL*	0*	1*	3*	BL*	0*	1*	3*
NCH001	4/ 3/'15	6/ 1/'15	44.3	13.0	17.4	12.8	62.2	125.4	83.6	83.0
NDE001	6/ 4/'15	7/29/'15	8.1	3.8	N/D	6.27	104.3	91.0	89.7	78.7
NDE002	8/ 5/'15	under treatment	6.3	N/A**	3.3	0.9	84.9	172.2	112.9	114.3
NDE003	8/17/'15	under treatment	5.1	-**	-**	-**	95.8	-**	-**	-**

*BL; baseline, 0; immediately after final treatment, 1; 1-month after final treatment, 3; 3-month after final treatment N/A**: Lab was unable to calculate; -**: No data collection

NDE001: Patient has relapsed and will be treated again off study on 1/5/'16

NDE003: Patient withdrew or was lost to follow-up on 10/14/'15 despite no adverse events

Source: Kaneka Pharma America's Interim Study Progress Report for New Enrollment Study for Liposorber LA-15 System

- Two adverse events (AEs) and 3 serious adverse events (SAEs) unrelated to the treatment have been reported. The observed AEs are evaluated as mild or moderate and are as follows: leg cramps, bacteremia, diarrhea, left mandibular pain and cellulitis of left hip area. All of the adverse events were deemed not related to the study by the principal investigator.

Table 4- Reported AEs and SAEs

	AE/SAE	Subject ID	Date occurrence	Description of AEs/SAEs	Severity*	Hospitalization	Relationship to treatment**
#001	AE	NCH001	4/ 6/'15	Leg cramps	Mild	-	Not
#002	SAE	NCH001	4/ 7/'15	Bacteremia	Mild	+	Not
#003	AE	NCH001	4/26/'15	Diarrhea	Mild	-	Not
#004	SAE	NCH001	5/ 6/'15	Left mandibular pain, R/O infection	Mild	+	Not
#005	SAE	NDE001	6/ 4/'15	Cellulitis of left hip area	Moderat	+	Not

*Severity; Mild, Moderate, Severe, Life-threatening, or Fatal
**Relationship to treatment; Not related, Unknown, or Related

Source: Kaneka Pharma America's Interim Study Progress Report for New Enrollment Study for Liposorber LA-15 System

At this time, there are no significant or new safety concerns.

2016 Update to the Systematic Literature on the Safety of the Liposorber LA-15 Device use in the Pediatric Population

Purpose

In preparation for the FDA PAC 2016 spring meeting, a systematic literature review was conducted to provide an update to address the following question: What adverse events are reported in the literature after treatment with the Liposorber LA-15 system, for any indication in the pediatric population (≤21 years old)? This is an update from the literature review presented at the Pediatric Advisory Committee (PAC) meeting on March 24, 2015.

Methods

On January 13, 2016, 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 November 1, 2014 (last date of search included in the previous literature review presented in PAC 2015) and January 13, 2016 (see Figure 1). The articles which report on adverse events associated with the device use in pediatric population for any indication were eligible to be included in this literature review. The search yielded 84 citations in PubMed, and 113 citations in EMBASE. After the exclusion of 74 duplicate records, there were a total of 123 articles.

To determine the eligibility of the articles, title, abstract and/or full text were reviewed. Of the 123 articles, none of them found to report adverse events associated with the use of Liposorber LA-15 in pediatric population. The reasons for exclusion are as follows: non-clinical study such as editorial, animal study, bench study, non-systematic review or guidelines (n= 41), no pediatric patients <21 years of age (n= 10), no use of the Liposorber LA-15 system or device not specified (n= 48), did not report on the presence or absence of adverse events (n=5); non-English (n= 4) or conference abstract (n= 15). As second phase of the review, the conference abstracts were reviewed to determine whether any safety data was presented. Of the 15 abstracts, only one found to include safety of the device in the pediatric population (Luirink, et al. 2015). The reasons for exclusion of the rest of the conference abstracts were as follows: no clinical data (n=3), no pediatric (n=1), no use of Liposorber (n=8) and device not specified (n=2).

Results

This literature review is an update of the review presented in the Pediatric Advisory Committee in 2015. It spans the period from November 1, 2014 to January 13, 2016. The search resulted in no article reporting on the adverse events associated with the use of Liposorber LA-15 in pediatric population for any indication. Due to the lack of any new publication on safety studies, as second phase of the review, we focused on the conference abstracts and evaluated if there was information on the safety with the device use. Fifteen conference abstracts were reviewed in detail, and one abstract, Luirink et al., reported on a study where Liposorber LA-15 system was used in 3 pediatric patients (aged 6 (girl), 10 (boy) and 11 (girl)) with homozygous familial hypercholesterolemia. According to the authors, LDL-apheresis was well tolerated; only mild side effects in 1 patient during the first 5 shifts (dizziness, shivering, mild nausea) were reported.

Conclusions

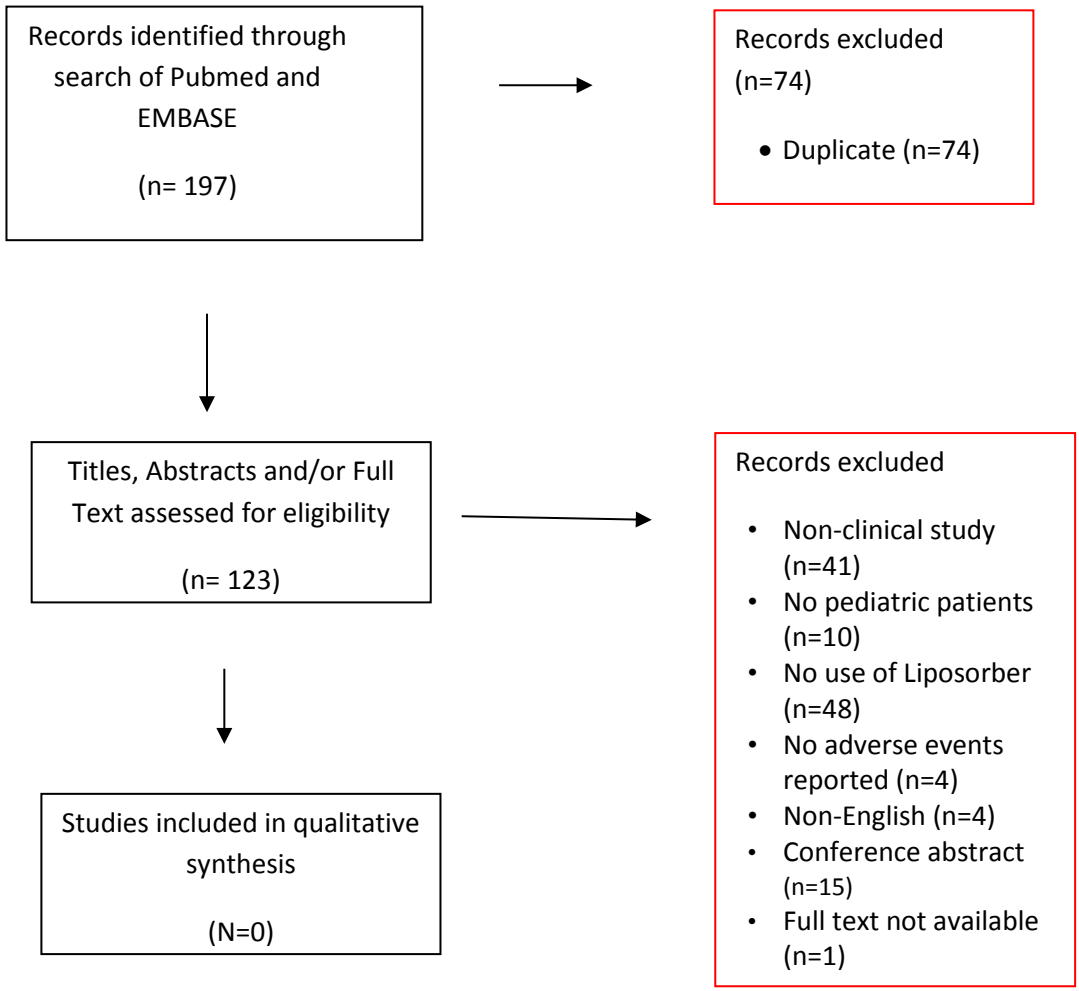
Based on the search criteria used, the literature update since November 2014 regarding pediatric use of the Liposorber LA-15 system did not result in any new study that reports on adverse events associated with the device use in pediatric population. However, only one conference abstract was identified that reported on mild side effects in 1 patients during the early course of treatment. The update of the literature review raised no new safety concerns.

Reference:

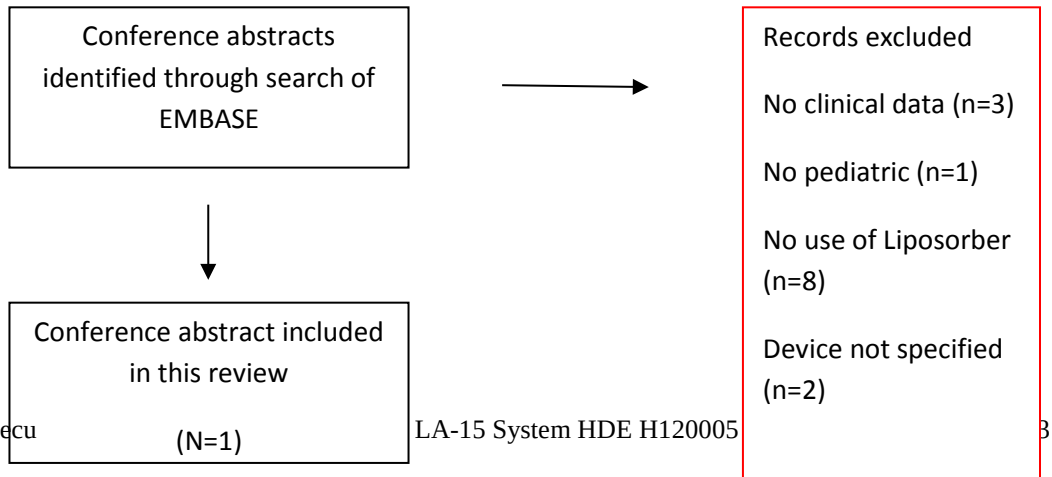
I. Luirink, A. Wiegman, B. Hutten and J. Groothoff (2015) *LDL apheresis in children with homozygous familial hypercholesterolemia: A case series*, Pediatr Nephrol (2015) 30:1543–1730

Figure 1- Article Retrieval and Selection

Phase 1- Review of peer reviewed literature:



Phase 2- Review of conference abstracts:



MEDICAL DEVICE REPORTS (MDRs)

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 SUS 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 actually caused a specific event can be difficult based solely on information provided in a given 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.
- SUS data is subjected to reporting bias, attributable to potential causes such as reporting practice, increased media attention, and/or other agency regulatory actions.
- SUS 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 4, 2016 utilizing the following search criteria:

- Product codes MMY (Lipoprotein, Low Density, Removal) and PBN (Apheresis for Focal Glomerulosclerosis in Pediatric Patients),
- Brand name (Liposorber), and
- A date range of November 1, 2014 to December 31, 2015.

The search resulted in 4 MDRs, 2 of which were not relevant to this analysis as they involved the Lacrifast device used for treating eye disorders. The 2 relevant MDRS were submitted by the manufacturer under the MMY product code, and did not involve pediatric patients, or patients undergoing apheresis for focal glomerulosclerosis.

Pediatric MDRs

As similarly reported in April 2015 at the prior PAC meeting for the Liposorber® LA-15 System, there were no MDRs submitted in the analysis period under product code PBN, or the HDE indication for apheresis for focal glomerulosclerosis in pediatric patients.

Patient Event Type Information

The event types for the 2 MDRs involving adult patients included 1 death and 1 serious injury. The 2 MDRs were submitted from Japan, and involved 1 male and 1 female patient. The patient problems reported included: death, apheresis, tachycardia, arrhythmia, Torsades-de-Pointes, and heart failure. Both reports indicated there was no known device problem associated with the patient events.

Death (n=1, 59 year old female). The patient was reported to have died after completion of her 6th LDL apheresis procedure, for treatment of arteriosclerosis obliterans. The time frame from the completed treatment and the patient death was not provided. As stated in the manufacturer narrative, "sudden aggravation of the patient's underlying disease(s) and or complication(s) may be responsible for the death and not relevant to the LDL-A treatment and use of the device".

Serious Injury (n=1, 83 year old male). The serious injury report, described a patient developing arrhythmia with Torsades-de-Pointes the day after treatment with the device. This was the patient's third completed treatment, with no reported issues. The patient was admitted to the ICU with worsening heart failure and elevated CPK isoenzyme levels. A coronary angiography was performed which did not note significant coronary stenosis. The patient was discharged with the "easing of his symptoms". Fifteen days after the initial event, the patient had another LDL-A treatment and "experienced cyanosis on peripheral limbs". His symptoms subsided and the LDL-A treatment was suspended. The manufacturer's narrative stated that a possible cause for the two

events included the increase in blood volume and plasma return at the end of the treatment, leading to an increase in heart load and the development of arrhythmia and worsening of transient heart failure. The manufacturer also provided another possible cause of the events as side effects of concomitant medication; although, all of the drugs used could not be confirmed. The patient's medical history included: arrhythmia, heart failure, and cardiovascular disease.

The patient problems reported (dyspnea, tachycardia, and arrhythmia), are known inherent risks with the use of this device, as indicated in the device's instructions for use (IFUs). It is difficult to determine if the patients' co-morbidities affected the outcomes following LDL-A treatment. The information contained in these two adverse event reports does not represent any new or previously unknown concerns regarding patient safety.

Historically, the number of MDRs submitted each year has been relatively small (i.e. ranging from 0-8 MDRs received per year). Additionally between 2003 and 2011, no MDRs were submitted. Consequently, receiving 2 MDRs over the past 13 months (the time period of this analysis) is consistent with past reporting trends.

VIII. SUMMARY

As of the January 2016 annual report provided by the sponsor, four patients with FSGS were entered into the study and were treated with the device. Our review of the published literature and received MDRs since the time of approval has not identified any new or unexpected risks for the pediatric population when compared to the premarket data. FDA concludes that the Liposorber LA-15 System for the indication of treatment in pediatric FSGS patients does not pose an unreasonable or increased risk of illness or injury, and that the probable benefit to health continues to outweigh the risk of injury or illness.

Therefore, FDA recommends continued surveillance and will report the following to the PAC in 2016:

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

IX. REFERENCES

1. Stefanutti C, Lanti A, Di Giacomo S, et al. Therapeutic apheresis in low weight patients: technical feasibility, tolerance, compliance, and risks. *Transfusion and apheresis science : official journal of the World Apheresis Association : official journal of the European Society for Haemapheresis.* Aug 2004;31(1):3-10.
2. Hudgins LC, Kleinman B, Scheuer A, White S, Gordon BR. Long-term safety and efficacy of low-density lipoprotein apheresis in childhood for homozygous familial hypercholesterolemia. *The American journal of cardiology.* Nov 1 2008;102(9):1199-1204.
3. Oto J, Suga K, Matsuura S, et al. Low-density lipoprotein apheresis in a pediatric patient with refractory nephrotic syndrome due to focal segmental glomerulosclerosis. *Journal of anesthesia.* 2009;23(2):284-287.
4. Stefanutti C, Vivenzio A, Colombo C, et al. Treatment of homozygous and double heterozygous familial hypercholesterolemic children with LDL-apheresis. *The International journal of artificial organs.* Feb 1995;18(2):103-110.
5. Stefanutti C, Notarbartolo A, Colloridi V, et al. LDL apheresis in a homozygous familial hypercholesterolemic child aged 4.5. *Artificial organs.* Oct 1997;21(10):1126-1127.
6. Stefanutti C, Di Giacomo S, Vivenzio A, et al. Low-density lipoprotein apheresis in a patient aged 3.5 years. *Acta paediatrica (Oslo, Norway : 1992).* Jun 2001;90(6):694-701.
7. Zwiener RJ, Uauy R, Petruska ML, Huet BA. Low-density lipoprotein apheresis as long-term treatment for children with homozygous familial hypercholesterolemia. *The Journal of pediatrics.* May 1995;126(5 Pt 1):728-735.
8. Palcoux JB, Atassi-Dumont M, Lefevre P, et al. Low-density lipoprotein apheresis in children with familial hypercholesterolemia: follow-up to 21 years. *Therapeutic apheresis and dialysis : official peer-reviewed journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy.* Jun 2008;12(3):195-201.
9. Dann EJ, Shamir R, Mashiach T, et al. Early-onset plasmapheresis and LDL-apheresis provide better disease control for pediatric homozygous familial hypercholesterolemia than HMG-CoA reductase inhibitors and ameliorate atherosclerosis. *Transfusion and apheresis science : official journal of the World Apheresis Association : official journal of the European Society for Haemapheresis.* Oct 2013;49(2):268-277.
10. Hattori M, Chikamoto H, Akioka Y, et al. A combined low-density lipoprotein apheresis and prednisone therapy for steroid-resistant primary focal segmental glomerulosclerosis in children. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* Dec 2003;42(6):1121-1130.
11. Bambauer R, Olbricht CJ, Schoeppe E. Low-density lipoprotein apheresis for prevention and regression of atherosclerosis: clinical results. *Therapeutic apheresis : official journal of the International Society for Apheresis and the Japanese Society for Apheresis.* Aug 1997;1(3):242-248.
12. Bambauer R, Schneidewind JM, Latza R. Apheresis technologies for prevention and regression of atherosclerosis: clinical results. *ASAIO journal (American Society for Artificial Internal Organs : 1992).* Sep-Oct 1999;45(5):403-407.

13. Keller C. LDL-apheresis in homozygous LDL-receptor-defective familial hypercholesterolemia: the Munich experience. *Atherosclerosis. Supplements.* Dec 29 2009;10(5):21-26.
14. Sachais BS, Katz J, Ross J, Rader DJ. Long-term effects of LDL apheresis in patients with severe hypercholesterolemia. *Journal of clinical apheresis.* Dec 2005;20(4):252-255.
15. Muso E, Mune M, Hirano T, et al. Immediate therapeutic efficacy of low-density lipoprotein apheresis for drug-resistant nephrotic syndrome: evidence from the short-term results from the POLARIS Study. *Clinical and experimental nephrology.* Jun 17 2014.