SUMMARY OF SAFETY AND PROBABLE BENEFIT (SSPB)

I.   **GENERAL INFORMATION**

Device Generic Name: High Density Lipoprotein Plasma Delipidation System

Device Trade Name: Plasma Delipidation System (PDS-2™ System)

Device Procode: QNB

Applicant's Name and Address: HDL Therapeutics, Inc.
                              601 21st Street, Suite 300
                              Vero Beach, FL 32960

Date(s) of Panel Recommendation: None

Humanitarian Device Exemption (HDE) Number: H190001

Humanitarian Use Device (HUD) Designation Number: HUD # 14-0331

Date of HUD Designation: August 25, 2014

Date of Notice of Approval to Applicant: December 1, 2020

II.   **INDICATIONS FOR USE**

The Plasma Delipidation System (PDS-2™ System) is indicated to reduce coronary artery atheroma in adult patients with homozygous familial hypercholesterolemia (HoFH) who are either inadequately responsive to or intolerant of maximal therapy for HoFH, including the latest medications and other device therapies approved by the FDA.

The indication for use statement has been modified from that granted for the HUD designation. The HUD designation was "to treat patients with homozygous familial hypercholesterolemia (HoFH)." It was modified for the HDE approval because of safety considerations and limitations of the clinical evidence provided, which necessitated that the device use be limited to treatment of patients who are either inadequately responsive or intolerant of maximal therapy for HoFH.

III.   **CONTRAINDICATIONS**

Standard contraindications related to plasmapheresis and plasmapheresis systems including:
- Patients who are in an actively septic state or are hemodynamically unstable
- Patients with heparin allergies should not receive heparin as an anticoagulant during plasmapheresis

- Patients with persistent hypocalcemia are at risk for worsening of their conditions because citrate is commonly used to prevent clotting and can potentiate hypocalcemia

Following are contraindications for the PDS-2 System:
- Patients with a known hyper-coagulable condition manifesting in history of highly suspected deep venous thrombosis or pulmonary embolism
- Patients with active cholecystitis
- Patients with unstable or uncontrolled hypertension
- Patients with unstable or uncontrolled insulin dependent diabetics

IV. **WARNINGS AND PRECAUTIONS**

The warnings and precautions can be found in the PDS-2 System labeling.

V. **DEVICE DESCRIPTION**

The PDS-2 System is a plasma processing system that is comprised of the following components:
(1) An automated processor (the hardware instrument with accompanying software),
(2) A sterile single use disposable kit (including the plasma delipidation set, solvent-in bag, solvent transfer set, and charcoal column), and
(3) Delipidation solvent mixture (sevoflurane and n-butanol).

The device treats autologous plasma separated from blood cells, collected from a patient via an approved plasmapheresis device. The plasma from the patient is collected into a sterile bag, which is then brought over to the PDS-2 hardware instrument for processing. The patient is not connected directly to the PDS-2 System. The patient's plasma is treated offline by the system (e.g., mixed with delipidation solvent mixture), filtered and pumped into an integral sterile bag, brought back to the patient's location, and then reinfused back into the patient via a separate standard infusion pump after processing. Each patient is limited to 7 weekly sessions of plasma treatments. Figure 1 shows the PDS-2 device with the disposable components.

Figure 1: PDS-2 Device with Major Components

The PDS-2 is hypothesized to reduce coronary artery atheroma by targeting a proposed mechanism by which cholesterol can be removed from cells (Brewer, 2011). In this article, the receptor ATP binding cassette subfamily A member 1 (ABCA1) was identified as a "gate" for allowing cholesterol to be released by cells. It was suggested that preβ-high-density lipoprotein (HDL) is the only form of HDL that can bind to the ABCA1 receptor, and the other form of HDL (α-HDL) cannot bind to this receptor. Thus, it is hypothesized that circulating preβ-HDL particles attach to the ABCA1 receptor site to enable reduction of cholesterol-laden plaques. The PDS-2 System is designed with the intent to target this hypothesized mechanism, (i.e., potentially increase the availability of preβ-HDL particles to enhance the body's delipidation capability and thereby reduce cholesterol-laden plaques). However, this proposed mechanism of action for this device has not been definitively proven in any non-clinical or clinical studies.

VI.   <u>ALTERNATIVE PRACTICES AND PROCEDURES</u>

Most patients with HoFH do not survive beyond 30 years of age without effective therapy to reduce the levels of low density lipoprotein cholesterol (LDL-C). As such, these patients are treated with aggressive therapeutics to attempt to dramatically lower their LDL-C levels. These treatments may include liver transplantation, LDL apheresis, or ileal bypass surgery. Additionally, there are approved devices, medications, and monoclonal antibodies for use in this population. These therapies have been shown to variably lower LDL-C levels.

Therapeutic options for patients with FH include:

Device Therapy:
There are two (2) devices approved for the treatment of patients with Homozygous FH (HoFH) or Heterozygous FH (HeFH):
1. Heparin-Induced Extracorporeal Lipoprotein (H.E.L.P.) System (PMA: P940016);
2. Liposorber LA-15 System (PMA: P910018).

The indicated populations for the H.EL.P. and Liposorber LA-15 devices are patients with either homozygous FH (HoFH) or heterozygous FH (HeFH). Both devices are indicated for removal of LDL-C.

The two (2) approved devices mentioned above, approved under PMA, are indicated for removal of LDL-C from plasma in high risk populations, including both heterozygous FH and homozygous FH. The PDS-2 System was determined to be appropriate for HDE given it is indicated to specifically treat only patients with HoFH and the device technology does not remove LDL-C, but is proposed to convert HDL particles.

To date, the benefits of the H.E.L.P. and Liposorber LA-15 devices outweigh the risks for patients with FH. However, the treatment schedules requires chronic maintenance of a central venous catheter, which does pose potential risk (e.g., infection, thrombosis, central venous stenosis) for patients.

Lifestyle Therapy:
- Weight loss
- Low fat diet
- Exercise

Medication Therapy: The following list includes those medications currently available for patients with either HoFH and/or HeFH (with highlight of more recent therapies) and is not necessarily a complete list):
- HMG-CoA reductase inhibitors
- Bile acid sequestrants
- Niacin
- Ezetimibe: FDA approved medication to reduce LDL-C and other lipids in patients with various types of hyperlipidemia, including HoFH. The drug is indicated as an adjunct to be used with statins.
- Liptruzet: Combination of ezetimibe and atorvastatin FDA approved to lower total cholesterol and LDL-C levels as an adjunct to other lipid-lowering therapies.
- Evolocumab: FDA approved medication indicated as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) for the treatment of adolescents and adults with HoFH or HeFH.
- Lomitapide: A microsomal triglyceride transfer protein (MTP) inhibitor that is FDA approved. An adjunct to dietary modification and other therapeutics to lower LDL-C.

- Mipomersen: An FDA approved medication that is an antisense oligonucleotide inhibitor that targets apolipoprotein B-100 (apoB-100). Approved as an adjunct to other regimens to reduce LDL-C and other lipids.
- Bempedoic acid: This FDA approved medication is an adenosine triphosphate-citrate lyase (ACL) inhibitor that reduces the hepatic synthesis of LDL-C. This medication is indicated for adults with HeFH only and as an adjunct to diet and maximally tolerated statin therapy.
- Alirocumab: A proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor that is FDA approved as an adjunct to diet and maximal statin therapy for adults with HeFH for the reduction of LDL-C.

VII. **MARKETING HISTORY**

The PDS-2 System has not been marketed in the United States or any foreign country.

VIII. **PROBABLE ADVERSE EFFECTS OF THE DEVICE ON HEALTH**

Below is a list of the potential adverse effects (i.e., complications) associated with the use of the device.
- Risks of any procedure involving extracorporeal circulation, including:
  - Abdominal discomfort
  - Anemia
  - Angina/chest pain
  - Arrhythmia
  - Blood loss
  - Bradycardia
  - Chills
  - Diaphoresis
  - Dyspnea
  - Fainting
  - Flushing/blotching
  - Headache
  - Hemolysis
  - Hyperventilation
  - Hypotension
  - Itching/hives
  - Lightheadedness
  - Nausea /vomiting
  - Pallor
  - Paresthesia due to citrate infusion
  - Shortness of breath
  - Tachycardia
  - Vasovagal reaction
- Vascular access problems, including:
  - Air embolism
  - Blood clotting

- o Excessive bleeding from the anticoagulant
- o Hematoma formation at the site of venipuncture
- Anemia
- Asthenia
- Coagulopathy
- Cyanosis
- Dizziness
- Fatigue
- Fever
- Fluid imbalance
- Generalized weakness
- Heart block
- Hyperkalemia
- Hypersensitivity reactions
- Infusion site pain
- Metal taste in mouth
- QT Interval abnormality
- Significant blood or plasma loss from extracorporeal circuit leaks
- Sweating
- If serum albumin is administered:
  - o Allergic reaction
  - o Transmission of infectious diseases

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. **SUMMARY OF NON-CLINICAL STUDIES**

A. Laboratory Studies

Biocompatibility Testing
Biocompatibility testing was conducted on the PDS-2 System, classified as an Externally Communicating Device – Blood Path, Indirect – Limited (≤ 24 hr.) Duration Contact, in accordance with 2016 FDA Guidance, *"Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process.' "* The total treatment time for all seven (7) treatment sessions is 7-9 hours/session, with 200 minutes of device contact per session.

The following testing was completed: cytotoxicity, sensitization, irritation/intracutaneous reactivity, acute systemic toxicity, material mediated pyrogenicity, genotoxicity, and hemocompatibility. The results of these evaluations supported that the PDS-2 System is biocompatible for its intended use.

Sterilization, Packaging, Simulated Shipping Distribution and Shelf-Life Testing of the Disposable Set

Sterilization
The Plasma Delipidation Sets, Solvent-In Bags, and Solvent Transfer Sets, are gamma sterilized. The validation of the gamma radiation sterilization was performed in accordance with ANSI/AMMI/ISO 11137-2: Sterilization of health care products – Radiation – Part 2: Establishing the sterilization dose. The full lot of disposable sets subject to a gamma sterilization level < 25 kGy were determined to be sterile to a Sterilization Assurance Level (SAL) of 10^{-6}.

Packaging
The PDS-2 Disposable Kit includes the Plasma Delipidation Set, the Solvent-In Bag, and Solvent Transfer Set. The sets pouch and/or kit tray integrity were validated after simulated shipping distribution and aging. Additionally, the package/product validation testing was successful.

Simulated Shipping Distribution
Environmental conditioning and simulated shipping distribution and transportation were performed on finished, packaged, sterilized devices in conformance with ASTM D4169-14, Standard Practice for Performance Testing of Shipping Containers and Systems and as recommended in ISTA Procedure 2A (2011), Partial Simulation Performance Test Procedure, Packaged-Products 150 lb (68 kg) or Less. All units passed the required performance testing and packaging maintained the integrity of the sterile barrier.

Shelf-Life Testing
The product and packaging shelf life of the PDS-2 disposables is 4 years. Aging was performed on finished, packaged, sterilized devices subjected to 2 years of real-time aging and an additional 2 year accelerated aging in conformance with ASTM F1980-07:2011, Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices. All units passed the required performance testing and packaging maintained the integrity of the sterile barrier.

Endotoxin Testing
The PDS-2 disposable kit is a single-use, gamma sterilized device. As the components of the kit come into direct contact with the patient's blood, bacterial endotoxin testing was performed in accordance with 2012 FDA Guidance, *"Guidance for Industry: Pyrogen and Endotoxins Testing: Questions and Answers."* Results of the bacterial endotoxin testing demonstrated that all device units were below the 20 endotoxin units per milliliter (EU) per device limit.

Aseptic Processing of the Solvents
The following tests demonstrated the aseptic processing of the solvents following the recommendations of the FDA's guidance document, Guidance for Industry Sterile

Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice (2004).

Table 1: Aseptic Processing Testing

Test Performed	Purpose	Applicable Standard	Conclusion
Bioburden Determination	The purpose of this test is to demonstrate that the starting concentration of microorganisms in the solvents used in the delipidation solution are not beyond the filter's ability to retain to ensure that purchased solvents continue to meet acceptable levels of microbial contamination for the proposed intended use.	ANSI/AAMI/ ISO 11737-1: 2018, Sterilization of health care products—Microbiological methods—Part 1: Determination of a population of microorganisms on products.	Bioburden testing will be conducted on every single lot of sevoflurane and n-butanol.
Bacterial Endotoxin	The purpose of this test is to demonstrate the starting concentration of bacterial endotoxin of the solvents used in the delipidation solution to ensure a final non-pyrogenic end-product.	USP <85> Bacterial Endotoxin Test.	Results of this testing demonstrated that both the n-butanol and sevoflurane contained less than 20 EU/mL.
Microbial Retention Testing of a Filter Membrane Assembly under Simulated-Use Conditions	The purpose of this study was to confirm the microbial retention properties of filter membranes under simulated use conditions.	ASTM F838-15a (2015) Standard Test Method for Determining Bacterial Retention of Membrane Filters Utilized for Liquid Filtration.	The filters effectively retained microbial challenge of *B. diminuta* after passage of the solvent.
Bubble Point Filter Integrity Testing	The purpose of this test was to confirm that the filter sterilizer is free of defects that may affect the microbial		These results demonstrated that the integrity of the 0.2 mm filters was not compromised by delipidation solvent

Test Performed	Purpose	Applicable Standard	Conclusion
	retention properties of filter membranes during use.		exposure and the filters retained their original retention properties.
Sterility Assay by Membrane Filtration Method – USP	This study determined whether the test article complies with the requirements for sterility, using the membrane filtration method.	United States Pharmacopeia 42, National Formulary 32, 2019. <71> Sterility Tests.	The test articles are considered sterile and meet the Membrane Filtration Sterility - USP requirements.
Bacteriostasis and Fungistasis by Membrane Filtration – USP	The bacteriostasis and fungistasis study evaluated the test article for inherent microbial properties using the membrane filtration method.	United States Pharmacopeia 42, National Formulary 32, 2019. <71> Sterility Tests.	Under the conditions of the study, the test articles are considered non-bacteriostatic and non-fungistatic.

Reprocessing Validation and Labeling

Manual Cleaning
Cleaning validation testing was performed to evaluate the cleaning efficacy of the recommended manual cleaning process. Devices were soiled and subjected to worst-case conditions of the cleaning procedure. A qualitative assessment (visual inspection) of device cleanliness and a quantitative assessment (residual protein and hemoglobin) were performed in accordance with 2015 FDA Guidance, "*Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling.*" The results of this testing satisfy the acceptance criteria for reusable medical devices and validate the recommended cleaning procedure for the device.

Table 2: Cleaning Validation Results

Parameter	Acceptance Criteria	Acceptance Result	Validation Result
Visual Inspection	"Visibly Clean"	**Pass**	**Pass**
Protein	$< 6.4 \ \mu g/cm^2$	**Pass**	
Hemoglobin	$< 2.2 \ \mu g/cm^2$	**Pass**	

Manual Low-Level Disinfection
The purpose of this study was to validate the low-level antimicrobial efficacy of the recommended disinfection process. The low-level disinfection efficacy was tested against indicator organisms per AAMI TIR 12:2010. Based on the evaluation criteria of a minimum of 6 Log10 reduction, the recommended disinfection process (CaviWipes® Disinfecting Towelettes) met the pre-determined acceptance criterion for

low-level disinfection and is considered effective for the HDL Therapeutics PDS-2 Device.

The recommended reprocessing validation instructions in the labeling are considered validated.

<u>Electrical Safety and Electromagnetic Compatibility (EMC)</u>
To minimize electrical and use hazards, the PDS-2 System was designed and tested to the standards below (**Table 3**). The device passed all testing requirements.

Table 3: Electrical Safety and Use Hazards Testing

Test	Results
IEC 60601-1 Issued: 2012/08/20 Ed: 3.1 Medical Electrical Equipment - Part 1: General Requirements for Basic Safety & Essential Performance	**Pass**
IEC 60601-1-2 ed3.0 (2007-03) Medical Electrical Equipment - Part 1-2: General Requirements for Basic Safety and Essential Performance - Collateral Standard: Electromagnetic Compatibility - Requirements and Tests	**Pass**
IEC 60601-1-6:2010 + A1:2013: Medical electrical equipment - Part 1-6: General requirements for basic safety and essential performance - Collateral standard: Usability	**Pass**
IEC 62366:2007 + A1:2014 Medical devices -- Application of usability engineering to medical devices	**Pass**
IEC 62304:2006 Medical device software -- Software life cycle processes	**Pass**
IEC 60601-1-2 ed. 4.0 Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral Standard: Electromagnetic disturbances - Requirements and tests	**Pass**

<u>Software</u>
Software documentation was provided in accordance with 2005 FDA Guidance, "*Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices*" and was acceptable.

<u>Non-Clinical Bench Performance Testing</u>
The purpose of these tests was to evaluate the non-clinical performance of the PDS-2 system. To test the mechanical integrity of the PDS-2 disposable kit, leak testing and tensile strength testing was conducted on non-sterile and sterile PDS-2 Disposable Kits and found to meet acceptance criteria.

To investigate the bench performance of the delipidation process, pilot studies were conducted that measured the levels of α HDL and pre-β HDL particles in the plasma following treatment with delipidation solvent. While these studies report changes in the plasma cholesterol particles, they do not specifically measure conversion of α HDL particles and pre-β HDL particles and do not directly support the hypothesis that the PDS-2 treatment is converting α HDL particles to pre-β HDL particles. In addition, some of the following tests were conducted on the bench with multiple delipidation

solvent mixtures, including that used in the PDS-2 system, but did not utilize the PDS-2
System.

Table 4: Bench Testing to Investigate Changes in Plasma Cholesterol Particles

Test Performed	Purpose	Method	Acceptance Criteria	Results
2D Gel Electrophoresis Study	Objective was to demonstrate *in vitro* that selective delipidation results in an increase in pre-β HDL in plasma and a reduction in α-HDL.	Human plasma samples were delipidated using a variety of delipidation solvent mixtures. Samples underwent 2D gel electrophoresis, immunoblotting for apoprotein A-I (apoA-I), and image analysis. (Note: The PDS-2 system was not utilized in this test.)	N/A	Test results suggest that pre-β HDL levels can be increased and α-HDL level is reduced by delipidation of human plasma using various delipidation solvent mixtures.
Enhanced Cell Efflux: Reverse Cholesterol Transport Assay Model	Objective was to investigate *in vitro* the cholesterol efflux activity of delipidated plasma compared to sham treated plasma and confirm that the cholesterol efflux activated by the delipidated plasma occurs via ABCA1 (rather than Scavenger Receptor class B type 1 (SR-B1)).	Human plasma samples were delipidated using a variety of delipidation solvent mixtures. Release of radiolabeled cellular cholesterol to isolated HDL acceptors, whole serum, or plasma was measured. Contribution of ABCA1 or SR-B1 was determined by comparing the release from cells lacking the receptor to that observed in parallel cell cultures expressing the receptor. (Note: The PDS-2 system was not utilized in this test.)	N/A	Selectively delipidated plasma using various solvent mixtures exhibited up to 27-fold increase in efflux activity compared to undelipidated plasma. Cholesterol efflux by selectively delipidated plasma was reported to occur preferentially via the ABCA1 transporter.
Selective Delipidation Process with the PDS-2	Objective was to conduct chemical analysis of	A total of five (5) pooled plasma batches were used in this study. Each	Plasma batches following selective delipidation profiled for:	**Pass**. Acceptance criteria met.

Test Performed	Purpose	Method	Acceptance Criteria	Results
	pooled human plasma batches that undergo the selective delipidation with the PDS-2 System for 60 seconds mixing time.	batch of plasma was delipidated with the PDS-2 for 60 seconds mixing time. Each unit was profiled before and after delipidation processing for chemical analysis of: full clinical chemistries, fibrinogen, PPL, TC, LDL-C, HDL-C, ApoA-I, ApoB, Trigylcerides and Free Cholesterol. Samples will also be tested via Gas Chromatography (GC) to determine levels of residual solvents (sevoflurane and n-butanol).	1. PPL - Avg. $\geq 80\%$ remaining mg/dL 2. TC - Avg. $\geq 80\%$ remaining mg/dL 3. LDL-C - Avg. $\geq 80\%$ remaining mg/dL 4. HDL-C - Avg. $\leq 60\%$ remaining mg/dL 5. ApoA-I - Avg. $\geq 80\%$ remaining mg/dL 6. ApoB - Avg. $\geq 80\%$ remaining mg/dL GC Analysis: 1. Resultant value of ≤ 25 ppm of Sevoflurane 2. Resultant value of ≤ 14 ppm of n-Butanol Qualitative review of plasma before and after delipidation processing by FPLC for PPL, TC, ApoA-I and ApoB.	

PPL = Phospholipid

TC = Total Cholesterol

LDL-C = Low-Density Lipoprotein Cholesterol

HDL-C = High-Density Lipoprotein Cholesterol

ApoA-I = Apolipoprotein A-I

Apo B = Apolipoprotein B

FPLC = Fast Protein Liquid Chromatography

Residual Solvent Testing

The acceptable residual levels of the solvent mixture in the plasma output are Sevoflurane ≤ 35.0 ppm and n-Butanol ≤ 20.0 ppm. The following testing measured the residual solvent levels remaining in the plasma after the delipidation process and prior to reinfusion.

Table 5: Residual Solvent Testing

Test Performed	Purpose	Acceptance Criteria	Results
Residual Solvent Analysis – African Green Monkey Study	The solvents remaining from the delipidation process were removed. The delipidated plasma was then tested, prior to infusion, using a gas chromatographic head space method, optimized for the detection of the two solvents.	Target residual solvent limits were <25 ppm (mg/L) Sevoflurane, <15 ppm (mg/L) n-Butanol.	**Pass**. Acceptance criteria met.
Residual Solvent GC Testing Summary – Human Clinical Trial	During the Acute Coronary Syndrome (ACS) clinical study (discussed below), all plasma samples from each batch of delipidated plasma were tested in triplicate using Gas Chromatography.	Release limits were 35 ppm for Sevoflurane and 20 ppm for n-Butanol.	**Pass**. Acceptance criteria were met.

X. SUMMARY OF CLINICAL INFORMATION

Two (2) clinical trials were conducted to evaluate the PDS-2 System. The trials included two (2), separate patient populations, as detailed below:
1. IDE trial G160070: Patients with Homozygous Familial Hypercholesterolemia (HoFH)
2. IDE trial G050263: Patients with Acute Coronary Syndrome (ACS)

Probable benefit and safety data from trial G160070 (patients with HoFH) was considered relevant for the proposed HDE application, while only safety data from trial G050263 (patients with ACS) was considered pertinent. While there are similarities in atheroma development in patients with ACS and HoFH, the review team posited that extrapolation of probable benefit data from trial G050263 was not feasible due to some differences in the pathogenesis of atheroma development in ACS compared to HoFH. Plaque formation in ACS requires a large lipid core but also features a significant accumulation of pro-inflammatory mediators while the deposition of lipids is the predominant factor in HoFH. However, due to the similar risk profiles of patients with HoFH and ACS, safety data from patients with ACS treated with the PDS-2 device could be extrapolated from patients with ACS to those with HoFH.

A. HoFH CLINICAL STUDY (G160070)

Study Design
The HALO-FH (HDL Acute Lipid Optimization in Homozygous Familial Hypercholesterolemia) study was conducted to assess the safety and probable benefit of the PDS-2 System in subjects with HoFH. Six (6) subjects at three (3) centers were enrolled in the study.

The first patient was enrolled on January 26, 2018 and study data collection through follow-up 2 weeks after the last infusion for the six (6) subjects was completed on August 31, 2018. Additional adverse event monitoring occurred for up to 12 months post-infusion. The study was terminated early based on the sponsor's assessment that statistically significant results were obtained. While noting the challenges of recruiting a large cohort for the premarket study, FDA strongly suggested enrolling a larger group of patients to enhance the quality and quantity of the clinical safety and probable benefit data.

Clinical Inclusion and Exclusion Criteria
Enrollment in the HALO-FH study was limited to patients who met the following inclusion criteria:
- Male or female subjects 12 years or older (U.S. sites)
- Male or female subjects 18 years or older (Canadian sites)
- Clinical diagnosis of HoFH due to a defect in the LDL receptor, or the identification of a defect in apoB-100 or a gain of function of PCSK9, or a genetic defect resulting in the HoFH clinical phenotype
- Females must be non-pregnant and non-lactating
- On a stable lipid lowering therapy for at least 4 weeks prior to enrollment
  - LDL cholesterol ≥ 300 mg/dl
  - Triglyceride ≤ 400 mg/dl
- Meet the criteria for serial plasmapheresis
  - Weight of ≥ 40 kg (90 lbs.)
  - Hemoglobin ≥ 12.5 g/dl
  - No other condition that would preclude the subject from successfully completing the series of plasmapheresis visits in the investigator's opinion
- Provide written informed consent before any study-specific procedures are performed. The subject (or legal guardian) must give consent by signing and dating an IRB approved consent form. A subject may be excluded for any reason that, in the Investigator's judgment, interferes with the ability to provide informed consent.
- Subjects must be willing to commit to completing all clinic visits and all associated procedures.
- *Angiographic Inclusion Criteria:* At least one coronary artery study segment will be identified for each subject and will remain constant throughout the study. The qualifying study segment(s) will have 20% to 40% stenosis as confirmed by coronary computed tomography angiography (CCTA).

Patients were not permitted to enroll in the HoFH study if they met any of the following exclusion criteria:
- Planned change in current lipid lowering therapy.
- Use of oral anticoagulants, unless the dose has been stable for 4 weeks.
- LDL or plasma apheresis within 1 week prior to enrollment and through 8-week primary endpoint CCTA.
- New York Heart Association (NYHA) class III or IV or last known left ventricular ejection fraction < 30%.

- Myocardial infarction, unstable angina, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), or stroke within 3 months of enrollment.
- Planned cardiac surgery or revascularization.
- Uncontrolled cardiac arrhythmia.
- Uncontrolled hypothyroidism.
- Uncontrolled diabetes.
- Participation in another investigational study actively or within 6 weeks prior to screening.
- Alcohol or drug use.
- Subjects with significant health problems in the recent past including blood disorders, cancer, or digestive problems.
- Known major hematologic, metabolic, gastrointestinal, or endocrine dysfunction.
- Pregnant or lactating women, women who had a pregnancy, regardless of outcomes, < 6 months prior to screening, or women who are unwilling to practice effective birth control or refrain from breastfeeding. Note: A urine pregnancy test will be performed at each screening and at each infusion visit on all premenopausal women.
- Active liver disease or hepatic dysfunction with liver enzymes [Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST)] > 3 times upper limit of normal of the reference range.
- Active cholecystitis, gall bladder symptoms, or potential hepato-biliary abnormalities defined as alkaline phosphatase > 3 times above the upper limit of the normal reference range. Note: subjects who have had a cholecystectomy are not excluded for this study.
- Currently undergoing renal dialysis or presence of renal dysfunction defined as GFR < 90 ml/min.
- Have had a previous adverse reaction to a low-osmolarity non-ionic intravascular iodinated contrast material injection, have asthma, or have any allergies that in the opinion of the investigator would exclude the patient from completing study required activities.
- Planned invasive surgery that would require a general anesthetic or a potential hospital stay during the study period.
- History of a bleeding diathesis, or evidence of active abnormal bleeding within 30 days before enrollment.
- History of intracranial hemorrhage, intracranial or spinal cord surgery, or central nervous system tumor or aneurysm.
- Current cancer (treated or untreated) at the time of screening date for this study
- Unstable or uncontrolled hypertension defined as two consecutive measurements (after at least 5 minutes of sitting) of blood pressure with systolic >180 mm Hg and/or diastolic >110 mmHg whether taking or not taking an acceptable concurrent antihypertensive medication.
- Severe valvular stenosis or regurgitation as defined by ACC/AHA criteria.
- History of major surgery < 2 weeks prior to enrollment.
- History of stroke < 3 months prior to enrollment.

- Unstable hypotension defined as two consecutive measurements of systolic blood pressure < 90 mmHg (a minimum of 30 minutes apart).
- History of illicit drug or alcohol abuse <1 year prior to screening.
- Life expectancy less than 1 year.
- Other conditions or criteria that, in the investigator's opinion, preclude the subject from participation.

Patient Demographics and Baseline Characteristics

Six (6) subjects were enrolled in the HALO-FH Study. The median subject age was 52 years (range 17-64 years). One subject (16.7%) was female and five (5) subjects (83.3%) were male. Five (5) subjects (83.3%) were white, zero patients were African American, and one subject was of other origin (16.7%). At screening, six (6) subjects had LDL cholesterol greater than 70 mg/dl and five (5) subjects had LDL cholesterol greater than 100 mg/dl. All six (6) subjects had HDL cholesterol greater than 32 mg/dl. **Table 6** below summarizes the subject baseline demographics.

Table 6: Subject Baseline Demographics and Medical History

Variable	Descriptive Statistics[1], N = 6
Age at time of screening (yrs)	52(16.4), 17-64
Height at screening (cm)	172.7(9.0), 160.3-182.9
Weight at screening (kg)	96.1(21.2), 60.3-110.2
Body Mass Index (BMI) at screening	30.8(7.8), 19.6-42.9
Male gender	5 (83.3%)
Childbearing potential	0 (0.0%)
Hispanic Ethnicity	1 (16.7%)
Race – White	5 (83.3%)
Race – Black or African American	0 (0.0%)
Race – Other	1 (16.7%)
Diabetes	0 (0.0%)
Hypertension	4 (66.7%)
Hypercholesterolemia	6 (100.0%)
Hypertriglyceridemia	0 (0.0%)
Peripheral Vascular Disease	1 (16.7%)
History of Smoking	4 (66.7%)
Family History Coronary Artery Disease	6 (100.0%)
Cerebral Vascular Disease	0 (0.0%)
Congestive Heart Failure	0 (0.0%)
Chronic Renal Insufficiency	0 (0.0%)
Prior Coronary Artery Bypass Surgery	1 (16.7%)
Prior Percutaneous Coronary Intervention	4 (66.7%)

Variable	Descriptive Statistics[1], N = 6
Prior Myocardial Infarction	2 (33.3%)
Xanthoma	3 (50.0%)
Location – Achilles Tendon	1 (16.7%)
Location – Ankles	0 (0.0%)
Location – Hands	1 (16.7%)
Location – Other	1 (16.7%)
Apheresis	2 (33.3%)
Every week	1 (16.7%)
Every two weeks	1 (16.7%)
Stable Angina at screening	2 (33.3%)
Unstable Angina at screening	0 (0.0%)
No Angina at screening	4 (66.7%)
Canadian Cardiovascular Society (CCS) Grading of Angina Pectoris I	4 (66.7%)
CCS II	1 (16.7%)
CCS III	0 (0.0%)
CCS IV	0 (0.0%)
CCS III/IV	0 (0.0%)
Heart Failure at screening	0 (0.0%)

[1]Median (standard deviation), minimum-maximum for continuous variables. Count (percentage) for count variables.

The baseline demographics are those expected for patients with HoFH. Notably, there was a significant history of cardiovascular disease.

Clinical Endpoints and Analysis
Following enrollment and screening, subjects were scheduled for 7 weekly treatments, each lasting 7-9 hours. At each treatment, subjects' plasma underwent selective HDL delipidation treatment utilizing the PDS-2. During each treatment, data was collected and there was observation for adverse events. Follow-up was conducted 2 weeks after the last infusion. Additional adverse event monitoring occurred at 3, 6, 9, and 12 months.

The primary endpoints of the trial were:
- Change in coronary atheroma area as assessed by coronary CT angiography in study coronary artery segments following serial infusions of autologous selectively delipidated HDL/pre-β enriched plasma following use of the HDL Therapeutics PDS-2 System as compared to baseline.
- Cumulative adverse events, serious adverse events, and unanticipated adverse device events from the start of infusion visit 1 to 8 weeks post-infusion visit 1, with the evaluated adverse events to include but not be limited to, hypotension,

Solvent B toxicity, hypoglycemia, hypocalcemia, and the major adverse cardiac events (MACE) of cardiac death, myocardial infarction, ischemic stroke, and revascularization of the vessel containing the study segment(s).

The secondary endpoints of the trial were:
- Change in total atheroma volume as assessed by coronary CT angiography in study coronary artery segments following serial infusions of autologous selectively delipidated HDL/pre-β enriched plasma following use of HDL Therapeutics PDS-2 System as compared to baseline.
- Cumulative adverse events, serious adverse events, and unanticipated adverse device events at 3, 6, 9, and 12 months post-infusion, with the evaluated adverse events to include but not be limited to major adverse cardiac events (MACE) of cardiac death, myocardial infarction, ischemic stroke, and revascularization of the vessel containing the study segment(s).

Results:
All six (6) patients completed seven (7) reinfusion sessions each for a total of 42 sessions.

Safety
Table 7 below summarizes the type and number of adverse events (AEs) observed during the HoFH study. Overall, 30 AEs were reported for five (5) subjects. Of the 30 reported events, 29 were classified as mild (96.7%) and one was classified as moderate (insomnia) (3.3%). None of the AEs were classified as severe. Only one (asthenia post-treatment) was considered to be potentially (possibly) related to the device.

Table 7: Adverse Event Summary for HoFH Subjects (n=6)

Type of Adverse Event	Number of Events	Device-related (DR) or Procedure-related (PR)
Metal taste in mouth	7	Probably PR
Asthenia post treatment	5	Possibly DR
Headache	2	1 Possibly PR
Generalized weakness	2	Probably PR
Vasovagal syncope	2	Possibly or Probably PR
Infusion site pain	2	Probably PR
Hot flush	1	Probably PR
Insomnia	1	Not DR or PR
Pain related to arm surgery	1	Not DR or PR
Occasional nocturnal dry cough	1	Not DR or PR
Cough with secretion	1	Not DR or PR
Pain in inferior limbs	1	Not DR or PR
High blood pressure	1	Not DR or PR
Neck pain	1	Not DR or PR
Lightheadedness	1	Not DR or PR
12 hr. post treatment fatigue	1	Probably PR

Patient vital signs were also measured during the HoFH study, including heart rate, respiratory rate, blood pressure, and body temperature. Clinical hypotension (systolic blood pressure < 90 mmHg or diastolic blood pressure < 60 mmHg) was observed during 32 (71.1%) of the 45 infusion visits. Clinical bradycardia (heart rate < 60 bpm) was observed during 27 (60.0%) of the 45 infusion visits and clinical tachycardia (resting heart rate > 100 bpm) was observed on 1 (2.2%) of the 45 infusion visits. Hypotension, bradycardia, and tachycardia were not considered to be adverse events by the investigator if no physical symptoms were present, and none featured physical symptoms. Additionally, no febrile episodes (body temperature ≥ 38°C and at least 1°C increase in body temperature from baseline) were observed. A summary of these vital sign fluctuations are shown in **Table 8** below.

Table 8: Vital Sign Summary for HoFH Subjects (n=6)

Vital Sign Monitoring	Number of Episodes
Hypotensive Episodes	32
Brachycardia	27
Tachycardia	1
Febrile Episodes	0

Finally, HoFH patients were followed every 3 months for up to 12 months after their last treatment. A summary of the follow up AEs is provided in **Table 9.** The majority of AEs observed were of mild severity and most resolved. None of the events were considered related to either the device or the clinical procedure.

Table 9: HALO-FH Study Adverse Event Follow-up Data (3, 6, 9, and 12 mo.) (n=4*)

Type of Adverse Event	Number of Events
Bronchitis	2
Light Sleep Apnea	1
Upper Tract Respiratory Infection	1
Anemia	1
Right Thumb Skin Mycosis	1
Feeling of Pressure Both Eyes	1
Increased Insomnia	1
Nose Squamous Cell Carcinoma in situ	1
Type 2 Diabetes	1
Back Pain	1
Neck Pain	1
Right Knee Pain	1
Enteritis	1
Arthritis L5-S1	1
Dorsal Spondylosis	1
Influenza	1
Thickening Left Achilles Tendon Xanthoma	1
Increased Headache Frequency	1
New Onset Exertional Chest Pain	1

*Complete AE follow-up data is only available for four (4) of the six (6) enrolled patients as two (2) patients withdrew from the study prior to completion of 12-month follow-up visits. One patient withdrew consent after the 6-month follow-up time point to participate in another trial. This patient did not report any AEs prior to study withdrawal. The second patient only participated in the 2-week follow up visit and did not report any AEs at that time. This patient did not wish to participate in any of the 3, 6, 9, and 12-month follow up visits and subsequently withdrew consent.

Patient vital signs, including systolic blood pressure, diastolic blood pressure, heart rate, and temperature were measured at the 3, 6, 9, and 12 month follow-up visits. There were no unexpected or concerning vital sign measurements observed during the follow-up period and all measurements were determined to be clinically insignificant as there were no symptoms associated with the changes in vital signs.

Probable Benefit:
Sixteen (16) plaques in six (6) patients were evaluated for atheroma cross-sectional area and volume. As shown in **Table 10** below, there was a statistically significant, 18% reduction (p=0.023) in the total atheroma cross-sectional area between baseline and 2 weeks after the last device treatment, which was the primary endpoint of the study. Additional exploratory analyses measured the plaque composition and volume. These results show that the reduction in total atheroma cross-sectional area was driven predominantly by a reduction of low-density (-38%) and necrotic core (-33%) portions of the plaque, known to be found in high-risk plaques prone to rupture and associated with increased rate of acute coronary syndrome. Similarly, evaluation of the secondary endpoint demonstrates that the volume of low density (-42%) and necrotic core portions (-35%) of the plaque were found to be reduced.

During the study period, 11/16 (69%) plaques regressed with respect to total area (i.e., reduction in total plaque area). When focusing on the highest risk low-density portions of the plaque and necrotic core portions of the plaques, overall, 14/16 (88%) experienced regression of these key components of the plaque.

Table 10: Summary Statistics and Testing Differences Per-Plaque

N=16 plaques mean ± SD	Baseline	Follow-up	Absolute change[a]	Relative change	P-value[b]
Atheroma cross-sectional area[c], mm^2					
Total	9.9 ± 3.5	8.2 ± 2.4	-1.8 ± 2.8	-18%	0.023[d]
Non-calcified plaque (NCP)	9.0 ± 3.5	7.2 ± 1.9	-1.8 ± 2.5	-20%	
Low-density NCP	1.6 ± 0.8	1.0 ± 0.5	-0.6 ± 0.6	-38%	
Necrotic core	1.5 ± 0.7	1.0 ± 0.5	-0.5 ± 0.6	-33%	
Fibrofatty	4.0 ± 1.9	3.2 ± 0.8	-0.8 ± 1.7	-20%	
Calcified	0.9 ± 0.9	1.0 ± 1.1	+0.1 ± 0.6	+11%	

N=16 plaques mean ± SD	Baseline	Follow-up	Absolute change[a]	Relative change	P-value[b]
Volume, mm³					
Total	180.4 ± 148.8	163.7 ± 168.9	-16.6 ± 48.5	-9%	
Non-calcified plaque (NCP)	157.6 ± 115.2	135.5 ± 117.7	-22.1 ± 35.8	-14%	
Low-density NCP	35.2 ± 38.1	20.6 ± 22.9	-14.6 ± 17.5	-42%	
Necrotic core	31.6 ± 32.2	20.4 ± 22.7	-11.2 ± 14.2	-35%	
Fibrofatty	67.1 ± 47.5	58.8 ± 51.6	-8.4 ± 22.3	-13%	
Calcified	22.8 ± 39.8	28.2 ± 59.0	+5.4 ± 21.7	+24%	

[a]Difference = Follow-up - Baseline
[b]Wilcoxon signed rank test (STATA 15.0)
[c]Area = plaque volume / plaque length
[d]The plaques were treated as independent observations.

HDL Particle Analysis
The device is proposed to convert α-HDL particles to pre-β HDL particles as one mechanism to increase the availability of pre-β HDL and the subsequent capture and removal of LDL-C from the bloodstream. As described in the HALO-FH IDE study (G160070) report, the sponsor conducted HDL particle analyses of plasma samples from the six (6) subjects in the study to investigate the ability of the device to convert α-HDL particles to pre-β HDL particles. Samples were obtained prior to and after seven (7) separate treatments with the device. A total of 36 plasma samples were received on dry ice and were run in a blinded and anonymized manner. This analysis was completed by Cardiovascular Nutrition Laboratory, Tufts University, Boston, MA and Boston Heart Diagnostics, a CLIA and CAP approved reference laboratory in Framingham, MA.

Plasma apolipoprotein (apo) A-I concentrations were measured by immunoassay (Roche Diagnostics) on a COBAS 501A analyzer. In addition, plasma was subjected to gel electrophoresis for the measurement of apoA-I in individual HDL particles. This method allowed for the quantitation of the percentage of apoA-I within very small preβ-1 HDL particles, small α-4 HDL particles, medium α-3 HDL particles, large α-2 HDL particles, and very large α-1 HDL particles. The results of the HDL particle analysis are in **Table 11**.

Table 11: Effect of Delipidated HDL Infusion on HDL Subparticles

Parameter	Pre-Infusion	Post-Infusion	Percentage Change	P, Post- vs. Pre-Infusion
Plasma apoA-I, mg/DL	114.10 (19.75)	91.60 (17.58)	-18.14 (8.76)	<0.0001
ApoA-I concentration in HDL subparticles, mg/dL				
α-1	30.66 (9.47)	22.51 (9.96)	-28.87 (19.09)	<0.0001
α-2	43.61 (10.17)	35.49 (8.45)	-14.64 (16.99)	<0.0001
α-3	16.49 (5.32)	12.18 (3.17)	-27.47 (21.18)	<0.0001
α-4	14.06 (4.46)	8.57 (3.29)	-33.97 (18.17)	<0.0001
Preβ-1	9.23 (2.35)	11.44 (4.22)	+31.69 (72.02)	0.007
ApoA-I percentage distribution in HDL subparticles, %				
α-1	25.89 (9.01)	23.98 (7.73)	-8.19 (16.21)	0.051
α-2	37.30 (5.57)	39.80 (6.72)	+3.12 (13.56)	0.087
α-3	13.98 (3.49)	12.43 (3.12)	-13.67 (16.61)	0.005
α-4	13.16 (2.98)	9.66 (2.81)	-16.62 (23.08)	0.001
Preβ-1	8.22 (1.87)	12.63 (3.43)	+65.92 (76.72)	<0.0001

*Data presented as median (interquartile range)

These results show a reduction in α-1, α-2, α-3, and α-4 subparticles with a concomitant increase in Preβ-1 subparticles, suggesting that the conversion of α to β HDL subparticles could be one mechanism by which the device helps to reduce circulating LDL-C.

B. **ACUTE CORONARY SYNDROME** (G050263)

A clinical study was conducted with the PDS-2 system in patients with Acute Coronary Syndrome (ACS). The objective of this trial was to evaluate the safety of the PDS-2 System. Probable benefit data from the trial in patients with ACS treated with the PDS-2 system could not be extrapolated to probable benefit data obtained in patients with HoFH treated with the PDS-2 device system based on differences in the pathophysiology of atheroma formation in the two (2) conditions. However, the safety data obtained in patients with ACS could be extrapolated to safety of patients with HoFH since the risk profiles of the two (2) conditions are relatively similar. Therefore, the ACS study safety results were evaluated as supplemental data to support safety in patients with HoFH. Fourteen (14) patients were treated between May 16, 2006 and January 29, 2008 at four (4) investigational sites.

Clinical Inclusion and Exclusion Criteria
Enrollment in the ACS study was limited to patients who met the following inclusion criteria:
- ≥ 18 years and ≤ 85 years of age;
- ACS diagnosis (defined as unstable angina or non-ST segment elevation myocardial infarction ((MI)) ≤ 14 days of screening and scheduled for clinically indicated coronary angiographic study;
- Subjects willing to commit to completing all clinic visits and the procedures associated with them;

- Meet normal inclusion requirements for plasmapheresis
  - Weigh 110 pounds or more
  - Hemoglobin greater than or equal to 12.5 g/dL;
- HDL ≥ 32 mg/dl and apoA-I level ≥ 95 mg/dL
- Triglycerides < 300 mg/dL
- Subjects had angiographic evidence of coronary heart disease in the "target artery" (not planned for PCI or coronary artery reconstruction) as defined by at least 1 lesion that has ≥ 20% but ≤ 50% reduction in lumen diameter by visual angiographic estimation within a segment of at least 30-80 mm in length. The target segment could have been designated as the target if it is accessible to intravascular ultrasound (IVUS) and had not undergone previous Coronary Artery Bypass Grafting (CABG). The target segment for IVUS was not to be an artery that has had a prior PCI. A single artery was to be identified as the target artery for each subject and remained constant throughout the study;
- Subjects were required to give written informed consent before any study-specific procedures were performed. The subject (or legal guardian) was required to give consent by signing and dating an IRB approved consent form. A subject was to be excluded for any reason that, in the Investigator's judgment, interfered with the ability to provide informed consent;
- Willingness to practice effective birth control and to refrain from breast feeding for women.

Patients were not permitted to enroll in the ACS study if they met any of the following exclusion criteria:
- An elevated ST segment MI ≤ 72 hours of screening procedures, as evidenced by:
  - Electrocardiogram (ECG) changes = ST elevations >2 mm in at least 2 contiguous precordial leads, or;
  - ST elevation of >1 mm in at least 2 limb leads, or;
  - >2 mm ST segment depression in V1, V2, or V2, V3 with reciprocal 1 mm ST elevation in II, AVF and V6, or;
  - Left bundle branch block not previously known to be present;
- Left ventricular function as evidenced by an ejection fraction (LVEF) < 40%;
- Subjects who were considered by their attending physician to be hemodynamically unstable, or who had active, ongoing ACS with ACS defined as unstable angina or non-ST-segment elevation MI;
- Left main coronary artery was not to have had a ≥ 50% stenosis by visual angiographic estimation;
- Pregnant or lactating women or women who had a pregnancy (regardless of outcome) ≤ 6 months prior to screening;
- Active liver disease or hepatic dysfunction (persistent liver enzymes [ALT and AST] > 3 times upper limit of normal of the reference range);
- Currently undergoing renal dialysis or presence of renal dysfunction defined as BUN or creatinine ≥ 1.5 times above the upper limit of normal reference range;
- Active cholecystitis, gallbladder symptoms, or potential hepato-biliary abnormalities defined as alkaline phosphatase >3 times above the upper limit of

the normal reference range. Note: subjects who had a cholecystectomy were not excluded from this study;
- Diagnosis of cancer (treated or untreated) < 5 years of screening date for this study (except for successfully resected basal cell carcinoma);
- Subjects who were insulin dependent diabetics;
- Unstable or uncontrolled hypertension defined as two (2) consecutive measurements (after at least 5 minutes of sitting) of blood pressure with systolic >180 mmHg and/or diastolic >110 mmHg whether taking or not taking an acceptable concurrent antihypertensive medication;
- Unstable hypotension defined as two (2) consecutive measurements of systolic blood pressure <90 mmHg;
- Cardiac insufficiency as defined by the NYHA classification as functional Class III or Class IV, as assessed by the investigator;
- History of illicit drug or alcohol abuse ≤ 1 year prior to screening;
- Active enrollment in another investigational drug or device study, or who have been previously enrolled in any cardiovascular drug or device study in the past 60 days;
- For subjects who were receiving chronic stable drug therapy for dyslipidemia, the dose was to remain stable for the study duration;
- Subjects who were currently taking Coumadin;
- Planned invasive surgery that required a general anesthetic or a potential hospital stay during the study period;
- Other conditions or criteria that, in the investigator's opinion, precluded the subject from participating for scientific, ethical, compliance, or subject safety reasons;
- Subjects with baseline IVUS images not meeting accepted IVUS core lab criteria were excluded.

Clinical Endpoints and Analysis
The primary endpoint was to evaluate the safety of the PDS-2 System. The secondary endpoint was to evaluate IVUS measurements to determine effectiveness.

Enrolled subjects underwent baseline catheterization with IVUS evaluation of a target artery with 20-50% stenosis, seven (7) treatment visits with the PDS-2 system, a follow up catheterization, and IVUS evaluation of the target artery at every 0.25 mm, 0.5 mm, and 1 mm.

Twenty-eight (28) subjects were enrolled in the study (14 placebo control, 14 PDS-2 treatment). The median subject age was 55 years (range 37 to 74 years). Six (6) subjects (21.4%) were female and 22 (78.6%) were male. Twenty-two (22) subjects (78.6%) were white, five (5) subjects (17.8%) were African American, and one subject (3.6) was of Pacific Islander origin.

Fourteen (14) patients in the treatment arm completed the study for a total of 98 plasmapheresis/reinfusion visits.

Safety Results
The safety results for the subjects in the PDS-2 treatment arm of the ACS Study are summarized in **Table 12**. Two (2) serious adverse events (SAEs) were reported for patients in the treatment group and two (2) SAEs were reported for patients in the placebo group. All were hospitalizations surrounding angiography or coronary revascularization, which were anticipated events. AEs were reported in seven (7) of the 14 patients treated with the PDS-2 System. While some AEs were related to the procedure (collection of or reinfusion of plasma), none of the AEs were deemed to be related to the device, with most being of mild severity and eventually resolving.

Table 12: Adverse Event Summary for ACS Study Subjects in the PDS-2 Group (n=14)

Type of Adverse Event	Number of Events	Related to Plasma Collection	Related to Reinfusion	Related to Device*
Hypotension	5	Probable	Not Related	Not Related
Heart block	3	3 Not Related	1 Not Related and 2 Remotely Possible	Not Related
Bradycardia	1	Probable	Not Related	Not Related
Hyperkalemia	2	Possible	Possible	Not Related
Revascularization, Percutaneous Coronary Intervention with drug eluting stent (Non Target Vessel)	1	Not Related	Not Related	Not Related
Other	2	Not Related	Not Related	Not Related
Cyanosis	1	Probable	Not Related	Not Related
Pallor	1	Probable	Not Related	Not Related
Peptic Ulcer	1	Not Related	Not Related	Not Related
Sweating	1	Probable	Not Related	Not Related

*AEs not related to the device were classified as "Anticipated" or "Subject/Non-Device Related" in the clinical study report.

Although there was a change in some blood chemistry values between the pre-initial plasmapheresis and final visit, all changes to the laboratory results were considered minor and not clinically significant. These results demonstrated that all reinfusion sessions were well tolerated by all patients.

Pediatric Extrapolation
In this premarket application, the sponsor originally provided the results of one pediatric patient (age 17 years) and proposed extrapolation of data from adults with HoFH to the pediatric population. A clinical reviewer (pediatric nephrologist) on the renal team presented the case to the agency Pediatric Extrapolation Device (PED) team and the PED team concluded that there was insufficient data to support extrapolation of data from adults for the pediatric patient population.

XI.   **FINANCIAL DISCLOSURE**

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The clinical study included three (3) investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XII.   **SAFETY AND PROBABLE BENEFIT ANALYSIS**

A. **Probable Benefit Conclusions**

The primary probable benefit endpoint of the premarket study for patients with HoFH was change in coronary atheroma area (compared to baseline) assessed by coronary CT angiography in study coronary artery segments following serial infusions of autologous selectively delipidated HDL/pre-β enriched plasma following use of the HDL Therapeutics PDS-2 System.

For the primary probable benefit endpoint, six (6) subjects each received seven (7) weekly treatments (infusions) of delipidated plasma. There was a statistically significant reduction in the total atheroma cross-sectional area between baseline and follow-up, mainly a result of a decline in the vital low-density and necrotic core portions of the plaque that are associated with increased rate of MACE. Among the 16 plaques evaluated, 14 showed a clinically significant reduction in either atheroma area or volume.

The premarket study results contained some uncertainty related to the low number (6) of treated subjects. However, the prevalence of HoFH is only about 1 per 1 million persons, for a total of about 300 in the United States. Since all of those patients would not be eligible for study inclusion based on logistical or other criteria, the review team concluded that the available data was adequate to assess the probable benefit of the device based on the consistent and clinically meaningful reduction of the vast majority of plaques evaluated.

B. **Safety Conclusions**

Adverse events (AEs) were compiled from two (2) separate studies: 1) Plasma Delipidation in Patients with HoFH (G160070); and, 2) Plasma Delipidation in Patients with Acute Coronary Syndrome (ACS; G050263). Probable benefit data from the trial in patients with ACS treated with the PDS-2 system could not be extrapolated to support probable benefit in patients with HoFH treated with the PDS-2 device system based on differences in the pathophysiology of atheroma formation in the two (2) conditions. However, safety data obtained in patients with ACS could be extrapolated to safety of patients with HoFH since the risk profiles of the two (2) conditions are relatively similar.

For subjects with HoFH, there were 30 AEs reported, occurring in five (5) of six (6) subjects. Among those, 29 (97%) were classified as mild and one (3%) as moderate (insomnia); none were considered to be severe. The most common AEs were transient and of minimal discomfort to the subjects. Only one (asthenia post-treatment) was considered to be potentially (possibly) related to the device. While some vital signs measurements were out of the normal range, none resulted in clinical symptoms. Finally, subjects with HoFH were followed every 3 months for up to 12 months after their last treatment. The majority of all AEs resolved during the study period and none were considered to be device- or procedure-related.

Among the subjects with ACS treated with the device, 14 subjects were treated for a total of 98 pheresis/infusion treatments. Among these 14 subjects, there were two (2) SAE; all were hospitalizations related to angiography or coronary revascularization (anticipated AE). The most common AEs were hypotension, heart block, and bradycardia. While some AEs were related to the procedure (collection of or reinfusion of plasma), none of the AEs were deemed to be related to the device, with most being of mild severity and eventually resolving.

Taken together, 20 subjects with either HoFH or ACS experienced a relatively low rate of device-related AEs and SAEs.

The review team initially concluded that while the safety profile for the device therapy in patients with HoFH was encouraging, the totality of the safety data was inadequate to support HDE approval. The sponsor proposed to extrapolate the safety data from subjects with ACS. The review team concurred since the underlying risk profile of patients with ACS was similar to that of patients with HoFH. While the clinical reviewers discussed the omission of vital signs abnormalities as AEs since these occurrences were asymptomatic, the reviewers concluded that none of the events were severe, and, given the patients' underlying cardiac disease, could not be determined to be device-related. This was supported by the fact that patients treated with the delipidation device are not exposed to an ongoing extracorporeal circuit, which is associated with hemodynamic compromise. Therefore, these events were very likely to be unrelated to the device.

C. **Probable Benefit-Risk Conclusions**

The probable benefits of the device are also based on data collected during the premarket study (G160070) of six subjects with HoFH to support HDE approval as described above. Patients with HoFH have a significantly shorter expected lifespan than the general population due to cardiovascular disease. Improved treatment options (e.g., medications such as Ezetimibe) for such patients are emerging but are still under investigation to determine if they can reduce early mortality. However, medication therapy must be continuous and engenders various side effects, including bleeding and gastrointestinal discomfort. The H.E.L.P. System (P940016) and the Liposorber LA-15 System (P910018) require long-term therapy and central venous access, thereby potentially exposing patients to risks such as infection, thrombosis, and central venous stenosis.

The plasma delipidation device offers an alternative therapeutic option for patients who are either unresponsive or intolerant of all other available medication or device therapies. Indeed, the indications for use requires that patients meet those strict criteria. Therefore, for patients with no alternative therapeutic options, this device meets an unmet need. The proposed treatment duration is one treatment per week for 7 weeks.

The premarket study results showed that treatment with the PDS-2 device significantly reduced atheroma (plaque) area while also reducing plaque volume after seven (7) weekly treatments (infusions) of delipidated plasma. There were clinically significant reductions in total atheroma (low density and necrotic core) cross-sectional area between baseline and follow-up. Since atheroma are major factors contributing to cardiovascular disease, there is a direct effect of the device on the pathogenetic factor associated with major adverse cardiac events (MACE).

As noted previously, AEs were compiled from two (2) studies (HoFH G160070, ACS G050263). Safety data obtained in patients with ACS were extrapolated to those with HoFH based on the similar, underlying risk profiles of the two (2) conditions. Overall, the safety profile of the device in 20 subjects with either HoFH or ACS was acceptable. There was no device-related SAE observed, and most AEs were mild or moderate. The other observed AEs were generally mild and largely resolved. The observation periods were adequate to fully assess the impact of the AEs. Taken together, 20 patients with either HoFH or ACS experienced a very low rate of SAE and only one device-related AE.

Assessing relatedness to a device or procedure in patients with serious diseases such as HoFH or ACS can be challenging since the underlying disease predisposes patients to alterations in vital signs or MACE. However, review of the AEs from both studies supports an acceptable risk profile.

There is uncertainty in the data due to the low number of subjects with HoFH who have been treated with the device. Six (6) subjects is a low number of subjects resulting in high uncertainty in the interpretation and generalizability of the results. However, the disease prevalence is very low (1 per million people) and many potential subjects were excluded based on the required criteria. The review team strongly encouraged recruitment and enrollment of more subjects, but those attempts by the sponsor were unsuccessful. Only 25% of patients screened were enrolled. The six (6) subjects represented about 0.02% (6/330) of persons with HoFH in the United States. By analogy, one could compare the subject enrollment to a hypothetical device study of patients with hypertension. Since about 45% of adults have hypertension based on current ACC/AHA criteria, enrolling 0.02 of those patients into a study would result in about 2.5 million subjects. Indeed, this is not a direct analogy, but enrollment into a trial is dependent on the relative prevalence and availability of subjects. Nevertheless, probable benefit data based on six (6) subjects is a limited set. The review team considered the inclusion of subjects with ACS into the probable benefit data set, but given the differences in disease pathophysiology, determined that the effectiveness data for patients with ACS could not be extrapolated to patients with HoFH. That said, the reduction of atheroma area, while not evident in each plaque, was

deemed clinically significant. The safety data included data collected on 20 subjects. While that data set was also relatively limited, the safety profile for all 20 subjects was favorable.

Due to the low number of subjects with HoFH in the G160070 premarket study, the review team is requesting a postmarket study, aimed to enroll 30 subjects. The added number of subjects will permit a more thorough assessment of the safety and probable benefits of the device system. Since HoFH is a severe and progressive disease that will definitely result in major adverse cardiac events and early mortality if left untreated, the potential of the device to attenuate poor outcomes and possibly ameliorate the disadvantages of alternative therapies were additional considerations in assessing benefit-risk.

1. Patient Perspective
   This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the HDE for this device.

In conclusion, although there is some uncertainty in the data due to small sample size, the current data along with additional considerations, including postmarket data collection, provide that the probable benefits of the device outweigh the probable risks. The review team believes that given the available information above, the data support that for reduction of coronary artery atheroma in adult patients with homozygous familial hypercholesterolemia (HoFH) who are either inadequately responsive to or intolerant of maximal therapy for HoFH, including the latest medications and other device therapies approved by the FDA, the probable benefits outweigh the probable risks.

D. **Overall Conclusions**

The data in this application support the reasonable assurance of safety and probable benefit of this device when used in accordance with the indications for use. There is an acceptable safety profile of the device system for patients with HoFH. The rates and severity of adverse events were relatively low. While 20 subjects is not a robust safety data set, the disease prevalence of HoFH is very low; therefore, while the quantity of safety data on subjects with either HoFH or ACS is low, the quality was robust and acceptable for the given probable benefit. The probable benefit of the device was established by a 13-42% reduction in non-calcified atheroma area and volume in 14 of 16 plaques.

In conjunction with the premarket data, a postmarket study will allow for a more thorough assessment of the safety and probable benefit for patients with HoFH who are either unresponsive or intolerant of alternative maximum and available therapy.

Therefore, the probable benefit to health from using the device for the target population outweighs the risk of illness or injury, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment when used as indicated in accordance with the directions for use.

XIII. **PANEL RECOMMENDATION**

This HDE was not taken to a meeting of the Gastroenterology-Urology Devices Panel because the information in this HDE did not raise any unanticipated safety concerns.

XIV. **CDRH DECISION**

CDRH has determined that, based on the data submitted in the HDE, the PDS-2 Plasma Delipidation System will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from using the device outweighs the risks of illness or injury. CDRH issued an approval order on December 1, 2020. The final conditions of approval cited in the approval order are described below.

1. The HDL Acute Lipid Optimization in Homozygous Familial Hypercholesterolemia (HALO-FHII) PAS is a prospective, multicenter, open-label new enrollment clinical investigation to provide ongoing safety and probable benefit assessment of the Plasma Delipidation System PDS-2, to reduce coronary artery atheroma in adult patients with homozygous familial hypercholesterolemia (HoFH) who are either inadequately responsive to or intolerant of maximal therapy for HoFH, including the latest medications and other device therapies approved by the FDA. The PAS will address the following questions:

    - What are the probable benefits of serial infusions of autologous selectively delipidated HDL/preβ-enriched plasma on coronary artery atheroma volume with the use of the HDL Therapeutics PDS-2 System?

    - Does the HDL Therapeutics PDS-2 System decrease the incidence of major adverse cardiovascular events (MACE)?

    - What is the safety profile of the HDL Therapeutics PDS-2 System, including the rate and severity of adverse events and changes in blood laboratory values?

    A total of 30 consented HoFH patients, aged 21 years or older, will be enrolled consecutively at up to 40 sites in the United States and will receive 7 weekly infusions of autologous selectively delipidated HDL/preβ enriched plasma following use of the PDS-2 System. Follow up clinical data will be collected at 2 weeks ± 7 days, 3 months, 6 months, 9 months, and 12 months after infusion seven (7).

    The primary safety endpoints are as follows: 1) The rates of serious adverse events (SAEs), and device-related and procedure-related adverse events from the start of infusion visit 1 through visit 7, and 1 week following infusion 7. The evaluated adverse events include, but are not limited to, hypotension, n-Butanol solvent toxicity, hypoglycemia, and hypocalcemia. 2) Laboratory values, specifically complete blood count parameters, comprehensive metabolic

parameters and lipid profile parameters before and after serial infusions of autologous selectively delipidated HDL/preβ enriched plasma following use of the HDL Therapeutics PDS-2 System as compared to baseline values. The primary probable benefit endpoint will be coronary atheroma volume, as assessed by coronary computed tomography angiography (CCTA), at 2 weeks ± 7 days and 6 months± 14 days after infusion visit 7 compared to baseline.

The secondary safety endpoints include the rates of SAEs, and device-related and procedure-related adverse events at 3 months, 6 months, 9 months, and 12 months after infusion visit 7. Other secondary endpoints include the rates of major adverse cardiac events (MACE) including cardiac death, myocardial infarction, ischemic stroke, and coronary artery revascularization at 3 months, 6 months, and 12 months after infusion visit 7.

From the time of study protocol approval, the following timelines must be met for the HDL Acute Lipid Optimization in Homozygous Familial Hypercholesterolemia (HALO-FHII) PAS:

- First subject enrolled within 6 months
- 20% of subjects enrolled within 12 months
- 50% of subjects enrolled within 18 months
- 100% of subjects enrolled within 24 months
- Submission of Final study report: 3 months from study completion (i.e., last subject, last follow-up date)

2. The HDL Therapeutics, Inc. Post-Approval Human Factors (HF) Study is a single arm prospective post-market human factors study to demonstrate that the system can be used by the certified operators, who are HDL employees, under both simulated and actual use conditions without producing patterns of use errors or issues that could result in a negative clinical impact to patients or harm to users or patients. The PAS will address the following question:

- Are the training and certification materials sufficient to ensure HDL employees are able to set up the device, prepare the solvents, and operate the device as indicated to generate a safe and effective delipidated plasma?

In this study, operators will be trained and certified according to the Employee Training Standard Operating Procedure (SOP-025-01). The study will be conducted with five certified operators (100% of device users). These certified operators will also be HDL employees. Operators will be observed during simulated use testing conducted in a laboratory environment and during the operators' first actual use case at a clinical site to ensure they can complete the required tasks.

In both simulated use and actual use cases, to evaluate each operator, an observer will document the operator's performance on critical tasks. The required critical

tasks for the PDS-2 will be dependent on the results from HDL's use-related risk analysis, and include but are not limited to the following tasks:

- Loading disposables and consumables,
- Preparation of the delipidation solvent mixture,
- Preparation of the solvent transfer set, and
- Transferring the delipidation solvent mixture to the solvent in-bag.

Study moderators will interview each participant to determine the root cause of any close calls, use difficulties, or use errors that are observed. An interim human factors validation report summarizing the observations and results after testing with two operators will be provided to FDA to ensure the data collected in the human factors study is adequate. A final human factors validation report summarizing the observations and results following completion of the study will be produced. The final human factors report for the PDS-2 System will be considered adequate if the human factors validation (summative) study evaluation yields results that:

1. Demonstrate that the device can be used by representative intended users under simulated and actual use conditions, without producing patterns of failures that could result in a negative clinical impact to patients or harm to users or patients;

2. Demonstrate that the device design, representative training and labeling are effective in mitigating all use-related risks to an acceptable level;

3. Demonstrate that no new use-related hazards or hazardous scenarios have emerged, and evidence supports that benefits outweigh the residual use-related risks; and

4. Demonstrate that operators are able to prepare the solvent mixture correctly, including verification of the mixture.

The PAS will not be considered complete until the above results are met in the final human factors report.

From the time of study protocol approval, the following timelines must be met for the HDL Therapeutics, Inc. Post-Approval Human Factors (HF) Study:

- Submission of an Interim study report on the first two operators within 3 months
- Study completion (with all operators) within 6 months
- Submission of Final study report: 30 days from study completion

In addition, the applicant must submit separate periodic reports on the progress of the HDL Acute Lipid Optimization in Homozygous Familial Hypercholesterolemia (HALO-

FHII) PAS and the HDL Therapeutics, Inc. Post-Approval Human Factors (HF) Study as follows:

- PAS Progress Reports every 6 months until subject enrollment has been completed, and annually thereafter.

- If any of the above milestones are not met, the applicant must begin submitting quarterly status reports (i.e., every 3 months), in addition to periodic (6-months) PAS Progress Reports, until FDA notifies the applicant otherwise.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. **APPROVAL SPECIFICATIONS**

Directions for use: See the device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. **REFERENCES**

1. Brewer, B.J., "The Evolving Role of HDL in the Treatment of High-Risk Patients with Cardiovascular Disease." *The Journal of Clinical Endocrinology & Metabolism*, Volume 96, Issue 5, 1 May 2011, pp. 1246–1257, https://doi.org/10.1210/jc.2010-0163