SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Embolization Agent, Vascular
Device Trade Name:	Embrace™ Hydrogel Embolic System (HES)
Device Product Code:	QVG
Applicant's Name and Address:	Instylla, Inc. 201 Burlington Rd North Building Bedford, MA 01730
Date(s) of Panel Recommendation:	None

Premarket Approval Application (PMA) Number: P250003

Date of FDA Notice of Approval: August 5, 2025

II. INDICATIONS FOR USE

The Embrace HES is indicated for embolization of hypervascular tumors in peripheral arteries ≤5mm.

III. CONTRAINDICATIONS

Embolization procedures should not be performed if:

- Patient is intolerant to occlusion procedures
- Vascular anatomy or blood flow precludes correct catheter placement or embolic injection
- Presence or likely onset of unresolvable vasospasm
- Known or suspected conditions that would prevent successful catheterization of targeted vasculature
- Presence of bilioenteric anastomoses or prior biliary interventions with stenting
- Presence of collateral vessel pathways which could potentially endanger non-target tissue
- Vascular resistance proximal to the feeding arteries precluding passage of Embrace HES into the lesion
- In large-diameter arteriovenous shunts (i.e. where the blood does not pass through an arterial/capillary/venous transition but directly from an artery to a vein) in the pulmonary vasculature
- Any neurovasculature or coronary location
- Known allergies to polyethylene glycol (PEG), ferrous compounds, tert Butyl Hydroperoxide, that are not amenable to pre-medication

- The safety and effectiveness of Embrace HES in pediatric patients and pregnant woman has not been established

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Embrace HES labeling.

V. DEVICE DESCRIPTION

The Embrace™ Hydrogel Embolic System (HES) is a polyethylene glycol diacrylate (PEGDA) based hydrogel that forms in blood vessels by delivering two aqueous precursor solutions, the Polymer Precursor and Initiator Precursor, via FDA-cleared microcatheters assembled to form a coaxial dual-lumen system, as described in the Instructions for Use.

The formed hydrogel acts as a vascular embolic by providing a mechanical barrier to blood flow. The Embrace HES is provided sterile and intended for single use only.

The Embrace HES is a biocompatible, hydrophilic, persistent, hydrogel produced from polyethylene glycol. The HES is available as a two-part system that forms *in situ* at the target location. Embrace is designed to offer controlled, targeted embolization utilizing the Instylla Microcatheter and Instylla™ Delivery Kit. The contents are described in **Table 1** and **Figure 1**.

Table 1. Embrace HES Contents

		Item	Description	Quantity
Accessory Kit		A	Syringe 1A – 3mL (Light Blue)	1
		B	Syringe 2A – 10mL (Yellow)	1
		C	Female-to-female Luer Connector	1
Precursor Kit		D	Vial 1C with attached Vial Spike	1
		E	Vial 1B with attached Vial Spike	1
		F	Vial 2B with attached Vial Spike	1
		H	Vial Holder	1

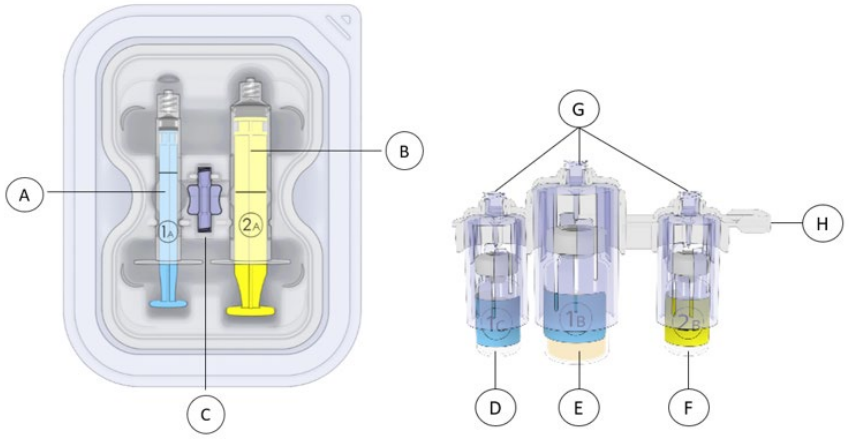

Figure 1. Embrace HES

Devices and Accessories Needed to Perform the Procedure

- Instylla Microcatheter (1.7F or 1.2F)
- Instylla Delivery Kit
- Commercially available microcatheter (inner diameter ≥0.027 inch for use with 1.7F Instylla Microcatheter or ≥0.021 inch for use with 1.2F Instylla Microcatheter) with guidewire
- Aqueous, non-ionic iodinated contrast medium (triiodobenzene-based) having ≥ 300mg Iodine per mL with viscosity less than 26 cP at 20°C
- 0.014" guidewire (for use with 1.7F Instylla Microcatheter) or 0.010" guidewire (for use with 1.2F Instylla Microcatheter)

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the embolization of hypervascular tumors. These include microspheres and particles. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Embrace Hydrogel Embolic System (HES) has not been marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

- Paralysis resulting from non-targeted embolization or ischemic injury from adjacent tissue edema
- Inadvertent embolization of a non-target vessel or territory
- Pulmonary embolism due to arterial venous shunting
- Thrombosis
- Ischemia, infarction, or tissue necrosis at an undesirable location
- Vessel or lesion rupture and hemorrhage
- Vasospasm
- Air embolism
- General edema
- Hypotensive crisis
- Embolization failure or recanalization requiring secondary intervention
- Foreign body reactions or infection necessitating medical intervention
- Complications related to catheterization (e.g., hematoma at the site of entry, clot formation at the tip of the catheter and subsequent dislodgment, nerve and/or circulatory injuries, or vessel trauma [e.g. dissection, perforation, rupture])
- Pain and/or rash, possibly delayed from the time of embolization
- Post-embolization syndrome

- Toxic or allergic reactions to embolic material
- Death

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

IX. SUMMARY OF NON-CLINICAL STUDIES

Engineering, biocompatibility, animal studies and sterilization testing were conducted on the Embrace HES as described below.

A. Bench Top Studies

Table 2 describe the bench top testing conducted at baseline and the shelf life of 2 years.

Table 2. Bench Top Testing

Study	Test Method	Acceptance Criteria	Results and Conclusions
Gel Time & Pot Life	No directly applicable Standard test method. Initiator Precursor was combined with Polymer Precursor. The gel time (time when Initiator Precursor was added until gel was formed) was determined. Pot life is the gel time measured three hours after the precursors are prepared.	The embolic materials must form a gel rapidly after 180 minutes of being constituted as Polymer Precursor and Initiator Precursor.	The gel time and pot life of the Embrace HES met the acceptance criteria.
Swelling	No directly applicable Standard test method. The Embrace HES was placed in water and allowed to incubate. The sample was removed from the water and weighed to obtain a final volume. Initial and final volume were used to calculate the swelling.	The HES samples shall not swell substantially over the course of testing.	The swelling of the Embrace HES met the acceptance criteria.
Modulus	No directly applicable Standard test method. A testing apparatus was utilized to compress the Embrace HES at a constant rate. The maximum force and sample height were recorded and used to calculate the modulus.	The modulus of formed hydrogel should be less than or equal to that of an artery under normal physiological pressures	The modulus of the Embrace HES met the acceptance criteria.
Viscosity	No directly applicable Standard test method. A rheometer was used to determine the viscosity of the Polymer Precursor.	Viscosity of Polymer Precursor to be less than the viscosity of lipiodol.	The viscosity of the Polymer Precursor met the acceptance criteria.
Dilution Sensitivity	No directly applicable Standard test method. Polymer and	The hydrogel embolic should not form/gel when diluted by blood	The dilution sensitivity of the Embrace HES

Study	Test Method	Acceptance Criteria	Results and Conclusions
	Initiator Precursors were diluted, and gel time was evaluated.	volumes in excess of embolic volume being delivered.	met the acceptance criteria.
Delivery Ease	No directly applicable Standard test method. The Embrace HES Polymer and Initiator Precursors were injected through the Microcatheter Delivery System (Instylla Microcatheter placed coaxially through an off-the-shelf (OTS) microcatheter). The maximum force for each injection was recorded and the Polymer and Initiator Precursor injection forces were combined to obtain a total injection force.	Two-part hydrogel embolic shall be easily delivered.	The delivery ease of the Embrace HES met the acceptance criteria.
Catheter Withdrawal	No directly applicable Standard test method. A distal portion of the Microcatheter Delivery System tip was inserted into a tubing fixture, and the Embrace HES was injected to embed it in gel. The distal portion was retracted from the gel at a constant rate.	Removal from formed hydrogel shall not cause catheter shaft break or permanent stretch deformation.	The catheter withdrawal of the Embrace HES met the acceptance criteria.
Embolic Persistence	No directly applicable Standard test method. Embrace HES samples were placed in a physiologic solution and monitored for degradation. The total days until full degradation was recorded.	Hydrogel embolic is persistent at body temperature for ≥ 30 days.	The persistence of the Embrace HES met the acceptance criteria.
In vitro Degradation	The degradation of the HES hydrogel at 37℃ and 55℃ was evaluated.	Hydrogel embolic is persistent at body temperature for ≥ 30 days.	The persistence of the Embrace HES met the acceptance criteria.
Syringe Marking	ISO 7886-1	10mL syringe: The fill volume shall be ±4% of the 8mL fill line. 3mL syringe: The fill volume shall be ±5% of the 1.5mL fill line.	The syringe markings of the Embrace HES met the acceptance criteria.
Vial Spike Compatibility	No directly applicable Standard test method. The Vial Spike was fully engaged into the septum of the vial, and the connected assembly was observed for any leaks.	Pre- assembled Vial Spike must be able to fully engage to the vial without leakage.	The vial spike compatibility of the Embrace HES met the acceptance criteria.

Study	Test Method	Acceptance Criteria	Results and Conclusions
Accessory Kit Compatibility	No directly applicable Standard test method. A filled Accessory Kit syringe was connected to the vial spike or female to female luer connector, and the assembly is observed for leaks.	Syringe prefilled with liquid must connect directly and securely to a Vial Spike or female-to-female luer connector and not leak during withdrawal of liquid.	The Accessory Kit compatibility of the Embrace HES met the acceptance criteria.
Simulated Use	No directly applicable Standard test method. An OTS microcatheter with guidewire was advanced through a model to the specified location. Coupled with a Tuohy Borst, the Instylla Microcatheter was coaxially placed through the OTS microcatheter until it exited the distal end of the OTS. The Embrace HES was delivered through the Coaxial delivery system.	Delivery of the hydrogel embolic creates an effective embolic while keeping non-target vessels patent.	The Embrace HES met the acceptance criteria for simulated use testing.
Particulate	USP <788>	The average number of particles present in the units tested does not exceed 6000 per container equal to or greater than 10 µm and does not exceed 600 per container equal to or greater than 25 µm.	Particulate count for the Embrace HES was determined to be acceptable
Shelf Life	The Embrace HES was evaluated per the testing listed above after accelerated and real time aging for 2 years.	See the collective acceptance criteria used for baseline testing listed above	The results of product functionality and packaging validation testing support a 2-year shelf life for the Embrace HES.

B. Biocompatibility

Embrace HES is classified as an implant device contacting circulating blood for a long-term duration (>30 days). For biocompatibility testing per ISO 10993 standards, the Embrace HES was in situ polymerized to simulate clinical use. Additionally, limited biocompatibility testing was conducted on the Embrace HES Precursor Solutions without polymerization, as the Embrace HES may not polymerize in clinical conditions with high flow, shunting, and/or reflux leading to increased exposure to Embrace HES precursor solutions. The following tests and assessments were conducted in support of the biocompatibility of the Embrace HES. Evaluation of the in situ polymerized Embrace HES

are summarized in **Table 3** below. Additionally, the limited biocompatibility evaluation of the Embrace HES Precursor Solutions is summarized in **Table 4** below.

- Bench and small animal biocompatibility testing per ISO 10993-1
- Implantation and thrombogenicity assessments were conducted in a chronic GLP Swine model
- Chemical characterization and toxicological risk assessments

Table 3. Biocompatibility Evaluation of the In Situ Polymerized Embrace HES

Description	Results
Cytotoxicity (ISO 10993-5) MEM Elution, 72-hour extract at 37°C. Serial dilutions of the in situ polymerized Embrace HES extracts were tested.	The 100% (undiluted) test article extract, and the 50% dilution caused severe cytotoxicity (Grade 4) and did not meet the requirements of the test since the grade was greater than a Grade 2. The test article was considered severely cytotoxic. In this testing, no cytotoxicity was observed at extract concentrations of ≤25%. An evaluation of the local tissue responses in the GLP animal studies was used to assess the clinical relevance of the in vitro cytotoxicity results. The in vivo GLP animal studies showed acceptable local tissue responses per clinical use. See Animal Studies section below.
Sensitization (ISO 10993-10) Guinea pig maximization sensitization test, normal saline and sesame oil extracts of in situ polymerized Embrace HES.	The test article extracts showed no evidence of causing delayed dermal contact sensitization in the guinea pig. The test article was not considered a sensitizer in the guinea pig maximization test. However, the unreacted Precursor Solution includes tert-butyl hydroperoxide which is a skin sensitizing compound[1]. See Table 4 Precursor Solution Biocompatibility Evaluation and discussion below.
Irritation (ISO 10993-23) Intracutaneous irritation test, normal saline and sesame oil extracts of in situ polymerized Embrace HES.	The test article met the requirements of the ISO intracutaneous reactivity test.
Acute Systemic Toxicity (ISO 10993-11) Acute systemic toxicity test, normal saline and sesame oil extracts of in situ polymerized Embrace HES.	There was no mortality or evidence of systemic toxicity from the extracts injected into mice. Each test article extract met the requirements of the study.
Material Mediated Pyrogenicity (ISO 10993-11) Material mediated rabbit pyrogen test, sterile nonpyrogenic normal saline extracts of in situ polymerized Embrace HES.	The test article met the requirements for the absence of pyrogens.
Bacterial Reverse Mutation (ISO 10993-3) Bacterial reverse mutation test, dimethyl sulfoxide (DMSO) and normal saline extracts of in situ polymerized Embrace HES.	The DMSO and saline test article extracts were considered to be non-genotoxic. However, the unreacted Precursor Solution includes tert-butyl hydroperoxide which is a genotoxic compound[1]. See Table 4 Precursor Solution Biocompatibility Evaluation and discussion below.

Description	Results
Mouse Lymphoma Assay (ISO 10993-3) Mouse lymphoma assay test, serum-free cell culture medium (RPMI0) and dimethyl sulfoxide (DMSO) extracts of in situ polymerized Embrace HES.	The RPMI0 and DMSO test article extracts did not produce a mean mutant frequency greater than the Global Evaluation Factor (GEF) of 90 mutants per 106 cells over the negative control mean mutant frequency either in the presence or absence of metabolic activation. The test article was considered to be non-genotoxic. However, the unreacted Precursor Solution includes tert-butyl hydroperoxide which is a genotoxic compound. See Table 4 Precursor Solution Biocompatibility Evaluation and discussion below.
Complement Activation Assay (ISO 10993-4) Complement Activation (SC5b-9 only) of the in situ polymerized Embrace HES.	The test article was not considered to be a potential activator of the complement system.
Hemolysis - *in vitro* Testing (ISO 10993-4) ASTM Hemolysis (Direct Contact and Extract Methods), in situ polymerized Embrace HES.	The supernatant for the direct contact and extract samples were observed to be light brown to brown for several of the replicates. As this color change was different than what is typically observed, the testing was terminated, and no conclusions were drawn. The HES precursor contains ferrous gluconate which can lead to a brownish color. As the method evaluates hemolysis as a function of color (i.e. absorbance at 540 nm), this color change could result in an inaccurate hemoglobin measurement; therefore, the testing was terminated prior to measurements and no conclusions were made. Therefore, the hemolysis endpoint for the HES cannot be addressed with the standardized in vitro hemolysis tests due to interference and incompatibility with the test article. An evaluation of the hematology in the GLP animal studies was used to assess hemocompatibility. There were no significant concerns for hemocompatibility in the chronic GLP animal studies. See Animal Studies section below.
Subacute, Subchronic, and Chronic Systemic Toxicity Chemical characterization of the in situ polymerized Embrace HES was conducted by exhaustively extracting the hydrogel and via a simulated use extraction per ISO 10993-18. Extracted substances were identified and assessed via a toxicological risk assessment per ISO 10993-17. The chemical characterization and toxicological risk assessment was conducted on a worst-case dose of 7.5 mL Embrace HES.	The toxicological risk assessment concluded that the risk of systemic toxicity from potential exposure to extracted chemicals was negligible for the worst-case dose of 7.5 mL Embrace HES. There were no significant concerns related to systemic toxicity in the chronic GLP animal studies. See Animal Studies section below.

Description	Results
Carcinogenicity Chemical characterization of the in situ polymerized Embrace HES was conducted by exhaustively extracting the hydrogel and via a simulated use extraction per ISO 10993-18. Extracted substances were identified and assessed via a toxicological risk assessment per ISO 10993-17. The chemical characterization and toxicological risk assessment was conducted on a worst-case dose of 7.5 mL Embrace HES.	The toxicological risk assessment concluded that the risk of carcinogenicity from potential exposure to extracted chemicals was negligible for the worst-case dose of 7.5 mL Embrace HES. However, the unreacted Precursor Solution includes tert-butyl hydroperoxide which is a genotoxic compound. See Table 4 Precursor Solution Biocompatibility Evaluation and discussion below.
Degradation Bench testing and the GLP animal studies were used to evaluate device degradation.	See Table 2 Bench Top Testing and Table 5 Animal Studies section below.

Chemical characterization of the Embrace HES was conducted by exhaustively extracting the hydrogel and via a simulated use extraction per ISO 10993-18. Extracted substances were identified and assessed via a toxicological risk assessment per ISO 10993-17. The toxicological risk assessment concluded that the risk of systemic toxicity and carcinogenicity from potential exposure to extracted chemicals was negligible for the worst-case dose of 7.5 mL Embrace HES.

Table 4. Biocompatibility Evaluation of the Non-Polymerized Embrace HES Precursor Solutions

Description	Results
Bacterial Reverse Mutation (ISO 10993-3) Bacterial reverse mutation test, Initiator Precursor Solution of Embrace HES.	The unpolymerized Initiator Precursor was considered to be mutagenic.
Sensitization (ISO 10993-10) Guinea pig maximization sensitization test, Initiator Precursor Solution of Embrace HES.	The unpolymerized Initiator Precursor showed no evidence of causing delayed dermal contact sensitization in the guinea pig. The test article was not considered a sensitizer in the guinea pig maximization test. However, the Precursor Solution includes tert-butyl hydroperoxide which is a skin sensitizing compound[1]. See discussion below.

Description	Results
Acute Systemic Toxicity Study in Mice (ISO 10993-11, modified protocol) The Precursors of Embrace HES were evaluated for acute systemic toxicity in mice. A 60X of clinical dose of both Precursors (Polymer Precursor followed by Initiator Precursor) was injected by the intravenous route via the lateral tail vein. Similarly, a separate group were dosed with saline as a control. Mice were observed for adverse reactions immediately after dosing the Polymer Precursor, immediately after dosing the Initiator Precursor, and at other time points up to 72 hours.	The unpolymerized Initiator Precursor met the requirements of the study since none of the mice treated with the test article showed a significantly greater reaction than the control mice. There was no mortality or evidence of systemic toxicity from the test or control article injected into mice. Additionally, no abnormal macroscopic findings of the viscera were observed, and weights of organs post-necropsy did not show any meaningful difference between test and control.

The Embrace HES may not polymerize in clinical conditions with high flow, shunting, and/or reflux leading to increased exposure to Embrace HES precursor solutions. Tert-butyl hydroperoxide is a component of the precursor solution.

Scientific literature supports that TBHP is sensitizing in animals[1], and sensitizers are capable of inducing a hypersensitivity reaction upon repeated contact (Clause 3.1 of ISO 10993-10:2021). A patient's susceptibility to a sensitization reaction is dependent on repeat exposure to the chemical. Therefore, although the Precursor Solutions were non-sensitizing in the GPMT study, the patient may be further exposed to TBHP with repeat device use and outside of the device use following the procedure. Therefore, communication of the potential health risks from exposure to TBHP is included in the labeling.

Scientific literature demonstrates TBHP is genotoxic in vitro and in vivo[1]. TBHP is a well-known oxidative DNA-damaging agent.

The instructions for use for the Embrace HES include procedures to minimize instances of non-polymerization of the HES, including the indications for use limiting to vessels ≤ 5mm and warning against use in conditions of high flow, shunting, and/or reflux.

As the potential for patient exposure to unpolymerized Embrace HES is not established, the clinical study included an evaluation of reporting of instances when the catheter was repositioned due to non-embolization to assess patient exposure to unpolymerized precursors. The rate of catheter repositioning due to non-embolization in HES was 3.0%.

The following warning is included in the labeling: "Tert-butyl hydroperoxide (TBHP), a component of the precursor solution, elicits genotoxicity and sensitization in animals." Additionally, a contraindication is included for patients with known allergy to TBHP.

C. Animal Studies

Table 5 describes the animal studies that were conducted to provide evidence of the safety and efficacy of the Embrace HES.

Table 5. Animal Studies

Description	Results
GLP Modified Acute Systemic Toxicity Study in Mice The Precursors of Embrace HES were evaluated for acute systemic toxicity in mice. A 60X of clinical dose of both Precursors (Polymer Precursor followed by Initiator Precursor) was injected by the intravenous route via the lateral tail vein. Similarly, a separate group were dosed with saline as a control. Mice were observed for adverse reactions immediately after dosing the Polymer Precursor, immediately after dosing the Initiator Precursor, and at other time points up to 72 hours.	The test article met the requirements of the study since none of the mice treated with the test article showed a significantly greater reaction than the control mice. There was no mortality or evidence of systemic toxicity from the test or control article injected into mice. Additionally, no abnormal macroscopic findings of the viscera were observed, and weights of organs post-necropsy did not show any meaningful difference between test and control.
GLP Subacute and Chronic Study to Evaluate the Local Tissue Effects of HES Precursor Delivery in the Swine Model The local effect of sequential HES Precursors delivery in the renal artery of swine was evaluated at 1-hour, 4-hour, 8-hour, 1-day, and 3-day time points (subacute) and 30day time point (chronic) as compared to a control group treated with saline and contrast.	It was concluded that for both the 3-Days (Subacute) and 30-Days (Chronic), after intra-arterial delivery in the porcine model the HES Precursors did not result in any systemic impact or local arterial tissue adverse response when compared to intra-arterial delivery of contrast/saline.
GLP Chronic Assessment of Embrace HES Material in the Swine Model The systemic impact of HES delivery was monitored during survival period in swine model in which one kidney and one liver segment was embolized per animal, and the impact of embolization to the target tissue was assessed after a 30-day animal survival period post-embolization.	Follow-up angiography and gross necropsy demonstrated that the HES did not migrate or exhibit non-target embolization. All five hepatic sites remained occluded through 30 days and two of five kidney sites had "light revascularization". There were no negative systemic effects over a 30-day survival period, and there was an anticipated local tissue response associated with embolization.
Chronic Study in the Rabbit Renal Models A rabbit renal study was conducted to evaluate the acute and chronic embolization effects of the HES in the rabbit kidney, as compared to a control embolic microsphere technology.	There were no adverse health effects and all treated animals survived to their scheduled time point, with the exception of two animals that were euthanized due to hind limb lameness. The study demonstrated acute and long-term embolization of targeted sites, comparable between test and control articles, and near complete degradation of the test article in the rabbit model by 26 weeks.
GLP Chronic Study of Embrace HES in the Rabbit Renal Model The embolic effect and vascular safety of embolization with the HES in the renal arteries of rabbits was evaluated as compared to a control embolic microsphere (control article) over 28, 90, and 180-days survival period.	Embrace HES versus Control Article treated kidneys showed similar responses to vascular occlusion. Hematological and clinical chemistry parameters were considered acceptable, as compared to the Control and normal values, at various time points in this chronic study.

Description	Results
GLP Study Evaluating Degradation in Rabbit Renal Model *In vivo* degradation assessments and local tissue responses to the Embrace HES were evaluated in the renal arteries of rabbits at 90, 180, 270 and 340 days.	After 340 days, targeted renal sites exhibited acute and long-term embolization durability, along with progressive degradation of the HES and no apparent systemic impact.
In vitro-in vivo Correlation (IVIVC) An IVIVC was established as a predictive model describing the in vitro/in vivo relationship between HES degradation.	A model between the in vitro and in vivo degradation of the Embrace HES was established, confirmed for validity, and challenged for input sensitivity (i.e., accelerated in vitro method ability to detect formulation changes). The established model provides a reasonable correlation between what is measured in vitro and what is expected as a vascular implant absorption/degradation time in the preclinical/clinical setting.

D. Sterilization

The Embrace HES will be sterilized at approved contract sterilization facilities. The HES Accessory Kit will be sterilized via ethylene oxide (EO) process and the HES Precursor Kit will be sterilized using moist heat. Both processes have been validated to a Sterility Assurance Level (SAL) of 10^{-6}.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the Embrace HES for embolization of hypervascular tumors in the US and Canada under IDE #G200149. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between March 5, 2021, and May 1, 2024. The database for this PMA reflected data collected through August 14, 2024, and included 150 patients. There were 22 investigational sites both in United States (US) and outside of US (OUS).

The study was a prospective, randomized (2:1), double-blinded multicenter clinical study to evaluate the Embrace HES for the embolization of hypervascular tumors as compared to standard of care (SOC) transarterial embolization/conventional transarterial chemoembolization (TAE/cTACE). The control group was in accordance with the treating investigator's standard of care and could include bland embolization products, ethanol or conventional TACE in combination with lipiodol. Drug-eluting beads were prohibited from use in this trial.

Tumor characteristics at baseline and local response following treatment were assessed according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) and RECIST 1.1. guidelines using CT (Multiphasic CT for hepatic tumors) or magnetic

resonance imaging (MRI) with images reviewed by an Imaging Core Laboratory. The same imaging modality/protocol (same machine preferred) was used throughout the study.

Throughout the duration of the study, subjects were clinically evaluated and assessed for adverse events using the grading of the NCI Common Terminology Criteria for Adverse Events (CTCAE Version 5.0). Severity of complications were further classified in accordance with Society of Interventional Radiology (SIR) guidelines. Following the embolization procedure, subjects were evaluated at discharge, 30, 90 and 180 days following the Index Procedure.

Safety data was reviewed and adjudicated by a Clinical Events Committee (CEC). The Data Monitoring Committee (DMC) was responsible for interim review of safety data and responsible for reviewing data from the sample size re-estimation analyses.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the Embrace HES study was limited to patients who met the following inclusion criteria:

1. Male or female subjects age ≥ 22 years old
2. Subjects with confirmed finding of hypervascular tumor on CT and/or MRI for whom TAE or cTACE is medically indicated, including but not limited to:
   i. Subjects with unresectable primary or metastatic hepatic cancer
   ii. Subjects with primary, metastatic or benign renal tumors
   iii. Subjects with bone metastases
   iv. Subjects with adrenal tumors
   v. Subjects with other hypervascular tumors
3. Subjects with at least one target lesion that is well-delineated such that, in the Investigator's opinion, the lesion can be measured in at least one dimension as 1 cm or more, suitable for remeasurement, and demonstrating definitive arterial enhancement. (Note: Pre-operative tumors do not need to meet this criterion.)
4. Subjects with at least one target vessel ≤ 5mm and Instylla HES can be delivered to the target vessel(s).
5. Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0-2 (PS 0-1 for metastatic disease)
6. Subject or authorized representative have been informed of the nature of the study and has provided written informed consent approved by the appropriate local Ethics Committee/Institutional Review Board and agrees to comply with all protocol-specified follow-up appointments.
7. Expected life expectancy ≥ 6 months after Index embolization

Patients were not permitted to enroll in the Embrace HES study if they met any of the following exclusion criteria:

1. Embolization for lesions other than hypervascular tumors such as arteriovenous malformations.
2. It is anticipated that not all target vessels requiring embolization during the index procedure can be embolized with either HES alone or the SOC embolization agent as assigned.
3. Undergoing radioembolization or DEB-TACE for Index procedure
4. Undergoing a planned secondary procedure the same day as the Index Procedure
5. Requires TAE/cTACE for liver tumors via extrahepatic collateral artery(ies)
6. Prior radioembolization of the target tumor lesion/vascular bed within 30 days of the Index Procedure.
7. For subjects with HCC or undergoing embolization to the liver: Child-Pugh Class C or presence of complete portal vein thrombosis.
8. Tumor lesions > 8 cm in diameter (in one direction) or >50% tumor volume burden of the target organ
9. If subject was treated with Avastin, last dose is within 4 weeks of the planned procedure.
10. Known severe atheromatosis or vascular anatomy that precludes catheterization
11. Presence of bilioenteric anastomoses and/or prior biliary stenting/drainage or any violation of the biliary sphincter, including sphincterotomy for embolization of liver tumors
12. Target lesion supplied by the pulmonary artery, coronary artery, or cerebral or cerebellar artery (requiring embolization of these arteries) or the artery to be embolized has connections to these arteries via a collateral pathway
13. Known allergies (based on history) to PEG, ferrous compounds, tert Butyl Hydroperoxide, contrast media or procedural sedatives/anesthetics that is not amenable to pre-medication
14. Uncorrectable impaired clotting: Platelet count <30,000/µL or International Normalized Ratio (INR) > 1.5
15. Serum creatinine > 2 mg/dL
16. Serum bilirubin level > 3 mg/dL
17. Serum albumin < 2.5 g/dL
18. Any contraindication to angiography or embolization protocol utilized at treating institution.
19. Pregnant or breast-feeding or females planning on becoming pregnant with the next 3 months (*women of child-bearing potential must undergo a pregnancy test performed in accordance with local institutional requirements*).

20. Other concurrent conditions including an ongoing adverse effect or complication of prior therapy or adverse drug reactions, that in the opinion of the Investigator or Clinical Events Committee, would be unlikely to receive clinical benefit from the study procedure or participation in the study may compromise subject safety or study objectives (including but not limited to ongoing acute infection, renal dysfunction, morbid obesity, severe cardiac disease).
21. Enrollment in a concurrent study in which the study treatment may confound the evaluation of the study device.

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 30 (± 7), 90 (± 14) and 180 (±30) days postoperatively. The follow up schedule is summarized in **Table 6**.

Table 6. Follow Up Schedule

Procedure	**Screening/Baseline Assessment *(within 45 days prior to planned vascular embolization)***	**Index Procedure *(Vascular Embolization)***	**Discharge**	**Follow-up: Day 30 ± 7 days and Day 90 ± 14 days**	**Follow-up: Day 180 ± 30 days (Remote visit unless in-person visit warranted)**
Demographic Information	✓				
Indication for Embolization	✓				
Disease Features[a]	✓				
Med./Surgical History/Current Status including Prior Therapies	✓				
CT Scan (Multiphasic CT for hepatic tumors) / MR at baseline and follow-up for assessment of radiologic response	✓			✓	
Targeted Physical Exam or Assessment[b]	✓		✓ (vitals only)	✓ (vitals only)	
EORTC QLQ-C30 and EORTC QLQ-HCC 18 (QLQ-HCC for hepatic subjects only)	✓			✓	✓
ECOG Performance Score/Child-Pugh Classification	✓			✓	

Procedure	Screening/Baseline Assessment *(within 45 days prior to planned vascular embolization)*	Index Procedure *(Vascular Embolization)*	Discharge	Follow-up: Day 30 ± 7 days and Day 90 ± 14 days	Follow-up: Day 180 ± 30 days (Remote visit unless in-person visit warranted)
Laboratory Testing [c]	✓			✓	
Pregnancy test for women of childbearing age	✓	✓			
RANDOMIZE		✓			
Angiography		Pre- and Post-Embolization Procedure	If clinically indicated		
Embolization Procedural Details		✓			
Concomitant Medications		✓	✓	✓	✓
Adverse Events (per NCI CTCAE Version 5.0) and severity rated in accordance with SIR guidelines; pain Numeric Rated Scale[d]		✓	✓	✓	✓

*The same imaging modality/protocol is to be used pre- and post-vascular embolization. Also, it is preferred that the same CT or MR system be used for the same subject for the duration of the study. If tumor is benign, baseline imaging can be taken within 60 days of Index procedure. Images for tumors collected as standard of care prior to the informed consent process but within 45 days (or 60 days for benign tumors) of Index procedure may be utilized as the baseline imaging.

[a]Tumor etiology, tumor location, tumor staging, number and dimension of tumor lesions (cm)

[b]At baseline, targeted physical examination including vitals (sitting blood pressure, pulse, respiratory rate, temperature, weight). At follow-up: Physical Assessment: including vitals (sitting blood pressure, pulse, respiratory rate, temperature, weight) to evaluate for changes from baseline. An in-person visit is preferred, but a remote (e.g., over the phone or via telehealth) visit can be substituted for select follow-up components if necessary.

[c]At baseline, complete blood count plus platelets, albumin, glucose, creatinine, AST/ALT, bilirubin, INR, and Alpha-fetoprotein levels in subjects with hepatic malignant tumors and Alkaline phosphatase for liver tumors. At follow-up, all baseline labs, excluding INR.

[d]Note: if subject was experiencing pain, the pain severity was to be scored using a Numeric Rated Scale where 0 represents no pain, and 10 represents the worst-possible pain

3. Clinical Endpoints

The primary safety endpoint was freedom from major adverse events (MAE) through 30 days post index procedure (as adjudicated by the CEC) compared with a literature-derived performance goal (PG) of 75%. The following events were considered MAE, if deemed by the CEC to be definitely or probably device and/or procedure-related and satisfied the criteria for a Grade ≥ 3 event in accordance with the SIR recommendations.

- Death
- Non-target embolization (NTE) of the index procedure, e.g., severe, intractable abdominal pain, gastroduodenal ulceration, intestinal ischemia, pancreatitis, cholecystitis AND angiographic/CT evidence of NTE
- Unintended target tissue ischemia (defined as symptomatic healthy/non-diseased tissue ischemia in the target organ)
- Pulmonary embolism
- Vascular injury requiring surgical/endovascular intervention

- Renal failure defined as increase in serum creatinine of ≥2mg/dL above baseline that persists to the Day 30 visit
- Hepatic failure (Grade 3+ asterixis, encephalopathy) that persists to the Day 30 visit
- Abscess in target organ/tissue: defined as clinical symptoms of infection (fever, leukocytosis, bacteremia), imaging consistent with the diagnosis of abscess, and a positive drainage culture
- Toxic and/or allergic reactions to the HES hydrogel manifested as immediate anaphylaxis or acute kidney injury (AKI - severe azotemia, oliguria, and/or anuria) with no other apparent etiology, e.g., contrast sensitivity.

The primary effectiveness endpoint of this study was technical success, defined as the successful delivery of the embolic agent to the index tumor feeding vessel, achieving stasis of flow, as characterized by the absence of contrast flow within the targeted vessel. This determination was made by independent radiologists (Core Laboratory) through comparison of pre- and final post-procedure angiograms. Stasis of flow, as defined, is an established metric for evaluating embolic devices per Society of Interventional Radiology (SIR) guidelines and aligns with the proposed indication for use of the device.

Subjects could contribute more than one effectiveness endpoint evaluation based on the number of target vessel embolizations. Target vessels were defined as a single discrete vascular bed. Sites captured and provided images to the Imaging Core Lab for independent assessment of a digitally subtracted angiogram (DSA), with a minimum frame rate of 2 frames per second, from contrast injection through clearance (about 5-10 seconds) before and after embolization. Per protocol, the DSA included arterial opacification and complete venous drainage of the intended target vessel.

If technical success of a target vessel could not be achieved with the assigned therapy, an ancillary (secondary) embolic agent could be used to complete the embolization procedure. If an ancillary (secondary) embolic was required to achieve successful embolization of the target vessel, this was considered a target vessel technical failure for HES only, regardless of determination by an independent radiologist. Multiple embolics could be used for standard of care treatment.

The primary analysis population for the primary effectiveness and primary safety endpoints was the Per Protocol (PP) population, which consisted of the modified Intent-to-Treat (mITT) population (those with a target vessel treated (i.e., embolic agent/chemoembolic agent delivered to target tumor)) who did not have any major protocol deviations that would impact the corresponding endpoint. Given the different timing of the primary effectiveness and primary safety endpoints (during procedure for effectiveness and through 30 days for safety), these endpoints were further evaluated in subgroups of the Per Protocol population, the Effectiveness Evaluable (EE) population and the Safety Evaluable (SE) population. The As Treated (AT) population includes mITT subjects, but analyzed according to treatment received rather than

treatment assignment. The mITT and AT populations were utilized as a secondary analysis population for primary effectiveness.

With regard to success/failure criteria, the study was considered a success if both the primary effectiveness and primary safety hypotheses were met.

B. Accountability of PMA Cohort

Between March 5, 2021 and May 1, 2024, a total of 182 subjects were consented in the study. Of these, 150 subjects were randomized, with 102 assigned to the HES treatment arm and 48 subjects to the control arm. Subject disposition for those who consented is shown in **Table 7**. Among the randomized subjects, 136 (91%) completed the 90-day Clinical Investigation Phase and 129 (86%) completed the Day 180 visit. Approximately 4% of subjects were lost to follow-up.

Table 7. Subject Disposition

	Hydrogel Embolic System (HES) N=102	Standard of Care TAE/cTACE N=48
Index Procedure	100.0% (102/102)	100.0% (48/48)
Completed 90-day visit	90.2% (92/102)	91.7% (44/48)
Completed Study [1]	86.3% (88/102)	85.4% (41/48)
Early Termination/Withdrawal	13.7% (14/102)	14.6% (7/48)
Subject non-compliant with protocol	0.0% (0/102)	2.1% (1/48)
Lost to follow-up	3.9% (4/102)	4.2% (2/48)
Investigator elected to withdraw subject [2]	2.9% (3/102)	0.0% (0/48)
Death	4.9% (5/102)	6.3% (3/48)
Other [3]	2.0% (2/102)	2.1% (1/48)

[1] A subject is considered to have completed the study if he/she completed all visits through Day 180 F ollow-up visit.
[2] Investigators elected to withdraw patients for the following reasons: (1) subject received liver transplant and was no longer necessary to follow the subject per standard of care, (1) subject was unhomed and non-compliant with study follow up, and (1) subject was medically complicated and mental status declined prior to study exit making them incapable of signing a revised consent.
[3] Other includes HES (1) Subject transferred to hospice care and withdrew from study, (1) site closed prior to subject's 180-day visit and SOC (1) subject experienced disease progression and was referred to Oncology for follow up.

C. Study Population Demographics and Baseline Parameters

Table 8 presents the demographic and baseline characteristics of the study population. The study population's demographic characteristics were well-balanced across treatment arms. The average age of participants was 65.4 years, with a slightly higher proportion of males

(56%). The population was predominantly white (79%), while 10% identified as Black/African American and approximately 5% as Asian. Additionally, the treatment arms demonstrated comparable measures for height, weight, and body mass index, further supporting the demographic consistency between treatment arms.

Table 8. Demographic and Baseline Characteristics

	Hydrogel Embolic System (HES) N=102	**Standard of Care TAE/cTACE N=48**
Age (years)		
Mean ± SD (N)	65.6 ± 12.37 (102)	65.1 ± 14.09 (48)
Median (Min, Max)	68.0 (31.0, 87.0)	68.5 (23.0, 81.0)
Gender		
Male	50.0% (51/102)	68.8% (33/48)
Female	50.0% (51/102)	31.3% (15/48)
Race		
American Indian or Alaska Native	1.0% (1/102)	0.0% (0/48)
Asian	4.9% (5/102)	4.2% (2/48)
Asian Indian	0.0% (0/102)	4.2% (2/48)
Other Asian	0.0% (0/102)	2.1% (1/48)
Black or African American	11.8% (12/102)	6.3% (3/48)
Chinese	2.0% (2/102)	0.0% (0/48)
White	75.5% (77/102)	85.4% (41/48)
Pacific Islander	1.0% (1/102)	0.0% (0/48)
Other	3.9% (4/102)	2.1% (1/48)
Ethnicity		
Hispanic or Latino	14.7% (15/102)	12.5% (6/48)
Not Hispanic or Latino	85.3% (87/102)	87.5% (42/48)
BMI (kg/m^2)		
Mean ± SD (N)	29.2 ± 6.42 (102)	28.8 ± 6.29 (47)
Median (Min, Max)	28.1 (16.3, 45.5)	27.5 (16.1, 43.2)

Table 9 summarizes the baseline characteristics for the mITT population, which were well-balanced across treatment arms, including the primary indications for vascular

embolization and prevalence of metastatic disease. Most subjects underwent vascular embolization for either definitive therapy for local tumor control (36%) or for addressing surgically unresectable or inoperable disease (23%). Preoperative embolization was the third most common indication, accounting for 13% of the population. Approximately 27% of subjects were treated for metastatic disease.

This was predominantly a non-smoking population. Consistent with protocol eligibility criteria, baseline ECOG performance scores were below 2, with ~95% of subjects having a score of 0 or 1. Additionally, there were very few cases of significant cardiovascular disease (NYHA Classification III or greater) or severe liver dysfunction (Child-Pugh Class C or higher).

Table 9. Baseline Tumor Characteristics

	Hydrogel Embolic System (HES) N=102	**Standard of Care TAE/cTACE N=48**
Smoking History		
Current Smoker	11.8% (12/102)	14.6% (7/48)
Past Smoker	32.4% (33/102)	35.4% (17/48)
Never Smoker	55.9% (57/102)	50.0% (24/48)
Primary Indication for Vascular Embolization		
Palliation	9.8% (10/102)	6.3% (3/48)
Definitive Therapy for Local Tumor Control (No additional therapy planned)	35.3% (36/102)	37.5% (18/48)
Surgically unresectable or inoperable disease	23.5% (24/102)	20.8% (10/48)
Preoperative Embolization for Curative Resection or Tumor Ablation	12.7% (13/102)	14.6% (7/48)
Bridge for Liver Transplantation	1.0% (1/102)	2.1% (1/48)
Downstage for Liver Transplantation	1.0% (1/102)	0.0% (0/48)
Control of tumor bleeding (non-traumatic organ infarct only)	2.9% (3/102)	0.0% (0/48)
Reduce risk of rupture	7.8% (8/102)	8.3% (4/48)
Other [1]	5.9% (6/102)	10.4% (5/48)
Being treated for metastatic disease		
Yes	27.5% (28/102)	25.0% (12/48)

	Hydrogel Embolic System (HES) N=102	Standard of Care TAE/cTACE N=48
No	72.5% (74/102)	75.0% (36/48)
Baseline ECOG Performance Score		
0	63.7% (65/102)	62.5% (30/48)
1	28.4% (29/102)	37.5% (18/48)
2	7.8% (8/102)	0.0% (0/48)
3	0.0% (0/102)	0.0% (0/48)
4	0.0% (0/102)	0.0% (0/48)
5	0.0% (0/102)	0.0% (0/48)
Not Done	0.0% (0/102)	0.0% (0/48)
Baseline NYHA Classification		
Class I	15.7% (16/102)	8.3% (4/48)
Class II	2.9% (3/102)	2.1% (1/48)
Class III	2.9% (3/102)	2.1% (1/48)
Class IV	1.0% (1/102)	0.0% (0/48)
N/A	77.5% (79/102)	87.5% (42/48)
Baseline Child-Pugh Classification		
A	54.9% (56/102)	60.4% (29/48)
B	7.8% (8/102)	2.1% (1/48)
C	1.0% (1/102)	0.0% (0/48)
N/A	36.3% (37/102)	37.5% (18/48)
[1] Other reasons include: HES (1) embolization for transplant consult, (1) preoperative, (1) reduce growth/pain syndrome, (1) locoregional therapy for tumor control, (1) repeat embolization, (1) definitive therapy, subject did not consider transplant and SOC (1) preoperative to reduce bleeding, (3) locoregional therapy for tumor control, (1) right proximal humerus lesion		

D. Safety and Effectiveness Results

1. Safety Results

The primary safety endpoint was freedom from major adverse events (MAE) through 30 days post index procedure (as adjudicated by the CEC) compared with a literature-derived performance goal (PG) of 75%. There were no unanticipated adverse device effects or adverse events designated as device-related only by the CEC. The primary safety endpoint met the goal with a rate of 99% (lower one-sided 95% CI= 95.15%).

The performance goal was met ($p<0.001$). Two MAE events occurred in the same subject, who developed an allergic reaction after HES embolization (increased heart rate, diaphoresis, and pallor, requiring epinephrine, albuterol, solumedrol, Narcan, and Romazicon), with subsequent development of a cool foot and access site arterial thrombosis the following day. Of note, the allergic reaction event was not classified as an MAE by the CEC as it resolved with pharmacological treatment.

The Primary Safety Endpoint analysis is presented in **Table 10**.

Table 10. Primary Safety Endpoint

	Hydrogel Embolic System (HES) N = 96	
	Number of Events N	**Number of Subjects with Events % (n/N)**
Primary Safety Endpoint Events [1]	2	1.0% (1/96)
Toxic and/or allergic reaction to HES hydrogel [5]	1	1.0% (1/96)
Non-target embolization of the index procedure	0	0.0% (0/96)
Unintended target tissue ischemia	0	0.0% (0/96)
Pulmonary embolism	0	0.0% (0/96)
Vascular injury requiring surgical/endovascular intervention [5]	1	1.0% (1/96)
Renal failure that persists to 30-day visit	0	0.0% (0/96)
Hepatic failure that persists to 30-day visit	0	0.0% (0/96)
Abscess in target organ/tissue	0	0.0% (0/96)
Death	0	0.0% (0/96)
Freedom from Major Adverse Events for 30 Days Post-Index Procedure		
Lower Limit of One-sided 95% CI [3]		95.15%

	Hydrogel Embolic System (HES) N = 96	
	Number of Events N	**Number of Subjects with Events % (n/N)**
p-value [4]		<0.001

[1] The primary safety endpoint includes MAEs deemed by the CEC to be definitely device and/or procedure-related or probably device and/or procedure-related and satisfies the criteria for a Grade ≥3 event, classified in accordance with the 2017 Society for Interventional Radiology (SIR) Guidelines..
[2] SE population includes mITT subjects who do not have major protocol deviations that impacts the primary safety endpoint identified for HES-treated subjects.
[3] One-sided 95% Clopper-Pearson exact confidence interval. The study device is considered to achieve the safety objective if the lower limit of the one-sided 95% CI is greater than the pre-specified performance goal of 75%.
[4] P-value is based on an exact binomial test comparing the proportion of subjects who are free from MAE to the performance goal of 75%. The hypothesis is evaluated at a one-sided 0.05 significance level.
[5] Both the MAEs occurred in the same subject. The subject developed an allergic reaction after HES embolization, characterized by increased heart rate, diaphoresis, and pallor, requiring administration of epinephrine, albuterol, solumedrol, Narcan, and Romazicon. The allergic reaction event was not classified as an MAE by the CEC as it resolved with pharmacological treatment. The subject developed a cool foot and access site arterial thrombosis the following day.

At least one adverse event was reported for 81.2% (82/101) of subjects treated with HES and 71.4% (35/49) of subjects treated with Standard of Care. Serious adverse events (SAEs) were reported in 30.7% (31/101) treated with HES and 18.4% (9/49) with Standard of Care. The majority of SAEs were unrelated to the device and/or procedure. Specifically, 47 of 52 SAEs (90.2%) in the HES arm and 15 of 16 SAEs (93.8%) in the Standard of Care arm were determined to be unrelated.

The severity of adverse events (AE)'s delineated by CTCAE grade was similar between the treatment arms. Grade 3 or greater AEs were reported for 36.7% of subjects in the HES arm and 30.6% in the Standard of Care arm. The most frequently reported AEs occurring through the Day 90 visit were abdominal pain (27% HES vs. 18% Standard of Care; p=0. 312), nausea (12% HES vs. 6% Standard of Care; p=0.387), fatigue (7% HES vs. 6% Standard of Care; p=>0.999) and post-embolization syndrome (11% HES vs. 8% Standard of Care; p=0.774). These symptoms/events were predominantly transient and typically occurred within the first few days following the study procedure which is consistent for patients undergoing TAE/cTACE.

The data do not show significant differences in the percent of subjects for whom Device and Procedure Related AEs were reported (28.7% for the HES arm and 22.4% for the Standard of Care arm, p=0.440) or Procedure Related AEs (25.7% for the HES arm and 16.3% for the Standard of Care arm, p=0.219). No subject in either treatment arm experienced a clinically relevant non-target embolization (NTE). Two (2) subjects treated with HES were reported to have experienced NTE with the events identified on the completion angiograms. These events were asymptomatic, did not require treatment and did not result in sequalae. The incidence of Serious Device and Procedure Related events was low for both treatment arms, 3.0% for HES, and 0% for Standard of Care, respectively. The incidence of Procedure only SAEs was identical for both treatment

arms at 2.0%. Of note, there were no device and/or procedure-related significant hepatic or renal complications leading to liver or kidney dysfunction, nor were there any reports of tumor abscess infarct or procedural-related mortality. Deaths were reported in 5 subjects (5%) in the HES arm and 3 subjects (6%) in the Standard of Care arm. All deaths occurred more than 30 days post-index procedure and were classified by the CEC as unrelated to the device or procedure, as the events were primarily associated with disease progression and/or comorbidities. Catheter repositioning due to non-embolization was evaluated to assess patient exposure to unpolymerized precursors. The rate of catheter repositioning due to non-embolization in HES was 3.0%.

Overall, the AEs observed in this trial are consistent with a patient population undergoing HVT embolization.

SAEs categorized as either Device and Procedure Related or Procedure Related only are summarized in **Table 11**. There were no device-related only SAEs. Device and Procedure Related SAEs were reported for 3% of subjects in the HES arm and none in the Standard of Care Arm. SAEs classified as Procedure-related only were reported in 2.0% of subjects in both treatment arms.

Table 41. Summary of Serious Device and Procedure Related Events

	Hydrogel Embolic System (HES) N = 101		**Standard of Care TAE/cTACE N = 49**	
	Number of Events N	**Number of Subjects with Events % (n/N)**	**Number of Events N**	**Number of Subjects with Events % (n/N)**
Total Number of Device and Procedure Related Serious Adverse Events	3	3.0% (3/101)	0	0.0% (0/49)
Immune System Disorders	1	1.0% (1/101)	0	0.0% (0/49)
Anaphylactic Reaction	1	1.0% (1/101)	0	0.0% (0/49)
Injury, Poisoning And Procedural Complications	2	2.0% (2/101)	0	0.0% (0/49)
Post Embolisation Syndrome	2	2.0% (2/101)	0	0.0% (0/49)
Total Number of Device Related Serious Adverse Events	0	0.0% (0/101)	0	0.0% (0/49)

	Hydrogel Embolic System (HES) N = 101		Standard of Care TAE/cTACE N = 49	
	Number of Events N	**Number of Subjects with Events % (n/N)**	**Number of Events N**	**Number of Subjects with Events % (n/N)**
Total Number of Procedure Related Serious Adverse Events	2	2.0% (2/101)	1	2.0% (1/49)
General Disorders And Administration Site Conditions	1	1.0% (1/101)	0	0.0% (0/49)
Generalised Oedema	1	1.0% (1/101)	0	0.0% (0/49)
Injury, Poisoning And Procedural Complications	1	1.0% (1/101)	0	0.0% (0/49)
Vascular Procedure Complication	1	1.0% (1/101)	0	0.0% (0/49)
Vascular Disorders	0	0.0% (0/101)	1	2.0% (1/49)
Hypotensive Crisis	0	0.0% (0/101)	1	2.0% (1/49)

2. Effectiveness Results

The primary effectiveness endpoint of this study was technical success, defined as the successful delivery of the embolic agent to the index tumor feeding vessel, achieving stasis of flow, as characterized by the absence of contrast flow within the targeted vessel. Non-inferiority of HES compared to Standard of Care was demonstrated using the pre-specified non-inferiority margin of 10%. The analysis for Technical Success was based on 132 vessels in 97 subjects treated with HES and 66 vessels in 48 subjects treated with Standard of Care. Technical Success, as assessed by blinded interventional radiologists (Core Laboratory), was achieved in 88.6% of the HES-treated vessels, and 77.3% of the Standard of Care-treated vessels (**Table 12**). Technical success (as determined by the independent radiologist) was not achieved due to incomplete stasis or the use of a secondary embolic. This represents a difference of 10.9% in favor of HES, with a two-sided 95% CI lower bound of -2.42% (p=0.001). Sensitivity analyses, including an analysis of all evaluable vessels and a tipping point analysis that considered unevaluable vessels as technical failures, confirmed non-inferiority of HES relative to Standard of Care. Subgroup analyses by gender and tumor location (hepatic vs non-hepatic) revealed no statistically significant differences in the primary effectiveness outcome across the evaluated subgroups.

Table 52. Primary Effectiveness Endpoint in EE Population

	Hydrogel Embolic System (HES)	Standard of Care TAE/cTACE	Difference [3] 95% CI	P-value
Target vessels in which Technical Success achieved [1] – EE Population [2]	88.6% (117/132) (N=97)	77.3% (51/66) (N=48)	10.9% (-2.42%, 24.28%)	0.001

[1] Subjects may contribute more than one target vessel, but only those vessels targeted for embolization prior to randomization are included in the primary effectiveness analysis. Technical success (as determined by the independent radiologist) was not achieved due to incomplete stasis or the use of a secondary embolic.
[2] EE population includes all mITT subjects who do not have major protocol deviations that would impact the primary effectiveness endpoint. mITT population includes all enrolled subjects who were randomized and have a target vessel treated. Data analyzed according to randomized treatment assignment. Per-protocol population includes mITT subjects who do not have a major protocol deviation. AT population includes mITT subjects, analyzed according to treatment received.
[3] Non-inferiority was assessed using a generalized estimating equation (GEE) model to obtain an estimate of the risk difference between treatments and its two-sided 95% confidence interval.

3. Subgroup Analyses

In the EE Population, a greater number of hepatic tumor feeding vessels (136 vessels) were embolized compared with non-hepatic tumor vessels (62 vessels). However, the number of vessels embolized in males and females were roughly equivalent, 105 vs. 93 vessels respectively. The statistical tests revealed that the p-values for the test of homogeneity across subgroups exceeded the predetermined significance threshold of 0.15. These findings indicate that there is no statistically significant evidence to suggest differences in the primary effectiveness outcomes across the evaluated subgroups for tumor location or gender. Results of these subgroup analyses are summarized in **Table 13**.

Table 63. Primary Effectiveness Endpoint Subgroup Analyses and Test for Homogeneity Proportion of Target Vessels with Technical Success

By Strata	Hepatic		Non-Hepatic		Test of Homogeneity P-value [4]
	Hydrogel Embolic System (HES) N=67	Standard of Care TAE/cTACE N=33	Hydrogel Embolic System (HES) N=30	Standard of Care TAE/cTACE N=15	
Target vessels in which Technical Success achieved [3]	87.1% (81/93)	76.7% (33/43)	92.3% (36/39)	78.3% (18/23)	0.656
By Sex	**Male**		**Female**		
	Hydrogel Embolic System (HES) N=48	Standard of Care TAE/cTACE N=33	Hydrogel Embolic System (HES) N=49	Standard of Care TAE/cTACE N=15	
Target vessels in which Technical Success achieved [3]	92.2% (59/64)	73.2% (30/41)	85.3% (58/68)	84.0% (21/25)	0.169

[1] Technical Success determined by a central independent radiologist via comparison of the pre- and final post-procedure angiograms.
[2] EE population includes all mITT subjects who do not have major protocol deviations that would impact the primary effectiveness endpoint.
[3] Subjects may contribute more than one target vessel, but only those vessels targeted for embolization prior to randomization are included in the primary effectiveness analysis.
[4] A test for homogeneity across strata or sex was performed with a GEE regression model utilizing a normal distribution with an identity link and strata or sex, treatment group and a stratum, or sex-by-treatment group interaction term. The p-value shown is for the interaction term and is assessed at a 0.15 significance level.

Tumor Response

The study demonstrated high tumor response rates across various lesion types, with comparable outcomes between treatment arms. In the EE population, following the index and any subsequent embolization procedures, both HES and Standard of Care achieved a 100% Disease Control Rate (DCR = complete response + partial response + stable disease) at Day 30 for non-hepatic embolized lesions (e.g., renal cell carcinoma, renal angiomyolipoma, bone tumors). By Day 90, the DCRs were 95.8% with HES and 80.0% with Standard of Care. For non-HCC hepatic embolized lesions (e.g., benign liver lesions, metastatic liver tumors), Day 30 DCRs were 88.9% with HES and 100.0% with Standard of Care, while Day 90 DCRs were 91.3% and 93.3%, respectively. In HCC embolized lesions, both treatment arms demonstrated favorable Objective Response Rates (ORR = complete response + partial response) and DCRs at Days 30 and 90. The Day 30 ORRs were 47.7% with HES and 50.0% with Standard of Care, and 45.5% and 56.5%, respectively, by Day 90. The Day 30 DCRs were 95.5% with HES and with Standard if Care it was 100%. DCRs at Day 90 were 90.9% with HES and 95.7% with Standard of Care.

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a 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 pivotal clinical study included 109 investigators of which 1 was full-time or part-time employees of the sponsor and 4 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 4
- Significant payment of other sorts: 0, None
- Proprietary interest in the product tested held by the investigator: 0, None
- Significant equity interest held by investigator in sponsor of covered study: 4

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Effectiveness of the device was demonstrated based data from non-clinical testing and a prospective, randomized (2:1), multicenter clinical study comparing Embrace HES versus standard of care (TAE/cTACE). The primary effectiveness endpoint was technical success, defined as the successful delivery of the embolic agent to the index tumor feeding vessel, achieving stasis of flow— characterized by the absence of contrast flow within the targeted vessel. The analysis for Technical Success was based on the Effectiveness Evaluable (EE) Population in which 132 vessels in 97 subjects were treated with HES and 66 vessels in 48 subjects were treated with Standard of Care. Technical Success was achieved in 88.6% of the HES-treated vessels, and 77.3% of the Standard of Care-treated vessels. The percentage difference favoring HES was 10.9%, with a two-sided 95% CI lower bound of -2.42%

(p=0.001). Non-inferiority of HES compared with Standard of Care was established using the pre-specified non-inferiority margin of 10%. Treatment effects were consistent across all analysis populations.

B. Safety Conclusions

The risks of the device are based on nonclinical and pre-clinical animal studies as well as data collected in the clinical study conducted to support PMA approval as described above. The safety of Embrace HES embolization was evaluated on the basis of freedom of major adverse events (MAE) compared with a literature derived performance goal (PG) of 75%. The MAE selected for this study were those considered most serious and concerning with TAE. Freedom from MAE was achieved in 99% of subjects (lower one-sided 95% CI= 95.15%) which met the PG (p <0.001). Two MAE events (allergic reaction and reintervention) occurred in the same subject. There were no unanticipated adverse device effects associated with the use of the Embrace HES and also no events specifically identified as related to the "device only" in either treatment arm.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. Tumor embolization is an effective and essential therapeutic strategy managing hypervascular tumors, aiding in symptom management and enhancing overall treatment efficacy and the Embrace HES is a safe and effective alternative to currently available embolic devices.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The use of the Embrace HES did not present any unknown risks that have not been previously described for transarterial embolization agents/devices. Adverse events reported in the course of the clinical study were not unexpected, neither in rate nor occurrence.

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 PMA for this device.

In conclusion, given the available information above, the data support that for embolization of hypervascular tumors in peripheral arteries ≤5mm, the probable benefits outweigh the probable risks when used in accordance with device labeling and the instructions for use (IFU).

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The findings from this study support the use of Embrace HES as a safe and effective alternative to existing embolization methods for treating various hypervascular tumors.

XIV. CDRH DECISION

CDRH issued an approval order on August 5, 2025. 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 device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

1. Tert-Butyl Hydroperoxide. Annex XV Restriction Report by The National Institute of Public Health and Environment (RIVM) (2008). https://echa.europa.eu/documents/10162/17228/trd_netherlands_tbhp_en.pdf/58159ba9-42b6-4d43-a29c-c182b8216127.