SUMMARY OF SAFETY AND PROBABLE BENEFIT (SSPB)

I. GENERAL INFORMATION

Device Generic Name: Intracranial Neurovascular Stent

Device Trade Name: River Stent System™

Device Procode: NJE

Applicant's Name and Address: Serenity Medical, Inc.
6 Cayuga Trail
Harrison, NY 10528

Date(s) of Panel Recommendation: None

Humanitarian Device Exemption (HDE) Number: H230002

Humanitarian Use Device (HUD) Designation Number: HUD # 2016-369

Date of HUD Designation: August 24, 2016

Date of Notice of Approval to Applicant: March 30, 2026

II. INDICATIONS FOR USE

The River Stent System™ is indicated for stenting of the venous sinus in adult patients (22 years of age or older) with idiopathic intracranial hypertension (IIH) who have failed medical therapy, have a significant stenosis of the venous sinus (> 50% stenosis and pressure gradient ≥ 8 mmHg), and have an upstream venous sinus diameter between 5 mm and 8.5 mm. Patients must also meet one or both of the following criteria:

- Intractable headache (severe impact with score > 59 on the Headache Impact Test (HIT)-6 scale) and papilledema or a history of papilledema and medical therapy failure for IIH for at least 6 months. Patients who are obese [body mass index (BMI) ≥ 30] must also have completed a weight management program including behavioral therapy, nutritional counseling, and/or medication support for at least 6 months, without achieving adequate relief of their IIH symptoms.
- Moderate to severe papilledema (Frisén grade ≥ 2), transient visual obscuration, or 6th nerve palsy who have failed medical therapy and in the opinion of the treating ophthalmologist are losing vision or at risk of losing vision.

The indication for use statement has been modified from that granted for the HUD designation. The HUD designation was for "stenting of venous sinus stenosis in patients

with idiopathic intracranial hypertension that have failed medical therapy." It was modified for the HDE approval because the revised indications for use (IFU) statement more clearly identifies the patient population in which the safety and probable benefit of the device is supported by the available clinical data. The patient population in the modified IFU falls within the patient population granted by the HUD designation.

III. CONTRAINDICATIONS

Use of the River Stent System is contraindicated for use in:

- Patients in whom anticoagulant, anti-platelet therapy or thrombolytic drugs are contraindicated.
- Patients with thrombophilic disorder or anticardiolipin syndrome.
- Patients with known hypersensitivity to nitinol and/or its components (e.g., nickel, titanium).
- Patients with known allergy to contrast or anesthetic drug despite pre-medication.
- Patients with anatomy that does not permit passage or deployment of the River Stent.
- Patients with an active bacterial infection.
- Patients with a pre-existing stent at the target transverse-sigmoid sinus.
- Patients with renal insufficiency not on dialysis.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the River Stent System labeling.

V. DEVICE DESCRIPTION

The River Stent System consists of a self-expanding, open-cell nitinol stent that is preloaded within the delivery catheter. The delivery catheter consists of the inner catheter and outer catheter subsystem which are two coaxial catheter assemblies.

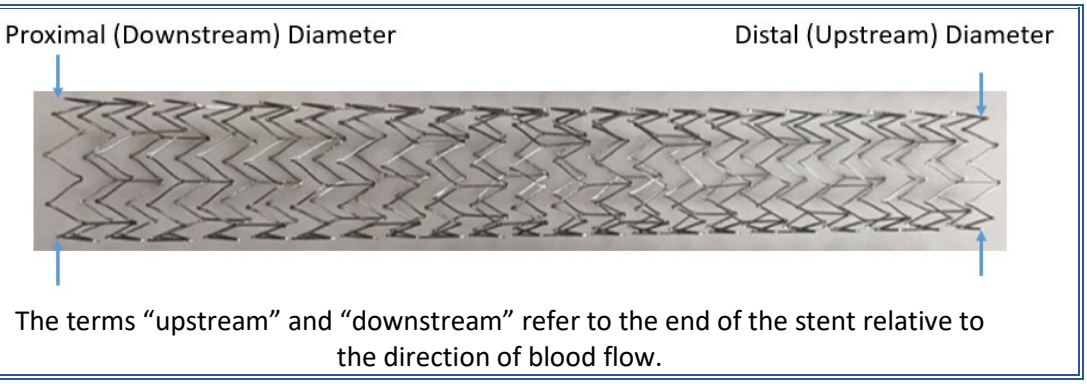


Figure 1: River Stent

The stent is 70 mm long and is provided in various proximal and distal diameters as shown in **Table 1**.

Table 1: River Stent Sizes

Stent Size	Length (mm)	Distal Diameter (mm)	Proximal Diameter (mm)
9 x 10.5	70	9	10.5
7 x 8	70	7.0	8.0
6 x 8	70	6.0	8.0

The River Stent delivery catheter is an over-the-wire system used to deploy the River Stent (**Figure 2**). The delivery catheter is guided to the target vessel over a guidewire and through a 6 French (F) guide catheter. Once positioned, the stent is deployed in the transverse sinus by withdrawing the outer catheter assembly while maintaining position of the inner catheter assembly. Radiopaque marker bands on the distal inner and outer catheter assemblies are visual indicators for stent deployment. The stent expands and conforms to the vessel wall upon deployment. The proximal end of the outer catheter assembly is a Y-hub with a rotating Tuohy hemostasis valve and a female Luer hub to allow flushing of the catheter. The same delivery system is used to deploy all stent sizes.

Fully Assembled River Stent System

Components of the River Stent System

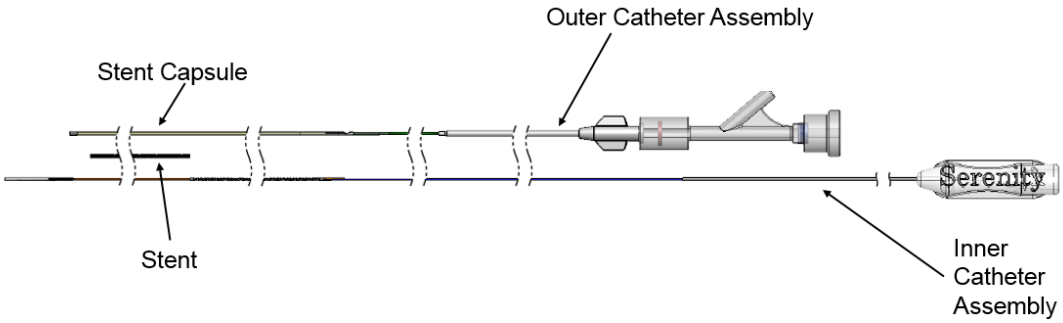


Figure 2: River Stent System

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Conventional procedures used in the treatment of IIH include addressing risk factors and comorbidity conditions, weight loss, and medication. For severe or refractory disease, interventions may include optic nerve sheath fenestration (ONSF) or cerebrospinal fluid (CSF) shunting.

VII. MARKETING HISTORY

The River Stent 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.

- Access site complications
- Allergic reaction to contrast agent, procedure medications, pre- and post-procedural medications (anti-platelet or anticoagulant agents), or nitinol
- Embolism (air, thrombus, device/stent or other)
- Death
- Headache
- Hematoma
- Hemorrhage/bleeding
- Infection
- Neurological insufficiencies including stroke and death
- Pain
- Renal insufficiency or failure secondary to contrast medium
- Thrombosis and stent restenosis or thrombosis
- Vessel injury (perforation, dissection, rupture, erosion, spasm or other)

Patients will experience radiation exposure from use of fluoroscopy during device delivery and computed tomography imaging procedures which may be used to visualize the vascular anatomy. Potential risks associated with radiation exposure may include, but are not limited to, alopecia, burns ranging in severity from skin reddening to ulcers, cataracts, and delayed neoplasia. The probability of adverse event occurrence increases as procedure time and the number of procedures increase.

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

IX. SUMMARY OF NON-CLINICAL STUDIES

A. Laboratory Studies

Objectives. The objectives of the laboratory studies were to conduct design verification and validation of the River Stent System, evaluate the biocompatibility, and validate the shelf-life and sterilization of the final, finished device.

Design Verification and Validation Testing

The devices used for testing were assembled and packaged in a controlled environment and subjected to sterilization. **Table 2** and **Table 3** below summarize the design verification and validation testing conducted on the River Stent System.

Table 2: Design Verification and Validation Testing of the River Stent System - Implant (Stent)

Test	Method	Results / Conclusions
Stent material	To evaluate the stent material composition	PASS
Austenite finish temperature	To measure the temperature at which a compacted stent achieves full self-expansion	PASS
Stent surface condition	To evaluate the stent surface condition	PASS
Corrosion resistance	To evaluate the corrosion resistance of the stent	PASS
Stent dimensions	To measure the stent length, proximal diameter and distal diameter	PASS
Stent percent surface area	To determine the percent contact area of a deployed stent with the vessel wall	PASS
Foreshortening	To measure the difference between the stent length in the delivery system and the stent length when deployed in a target vessel	PASS
Stent deployment accuracy	To measure the difference between the deployed position and intended deployment position of the stent within a target vessel	PASS
Stent integrity	To visually evaluate the ability of the stent to resist delivery-related damage after simulated deployment	PASS
Radial force	To measure the resistive force of the stent to radial compression	PASS

Test	Method	Results / Conclusions
Mechanical properties	Characterization testing performed to determine tensile and fatigue properties as inputs to support stress/strain and fatigue analysis	PASS
Stress/strain analysis and factor of safety analysis	Characterization testing via finite element analysis performed to determine maximum stresses and strains within the device to support fatigue analysis	PASS
Stent durability	To evaluate stent durability after 10 years of simulated use	PASS
Stent radiopacity	To evaluate radiopacity of stent for visibility during and after device delivery	PASS
Magnetic resonance imaging (MRI) compatibility	To evaluate stent safety and compatibility with MRI for MR Conditional labeling	PASS

Table 3: Design Verification and Validation Testing of the River Stent System - Delivery System

Test	Method	Results / Conclusions
Particulate	To measure the particulate shed by the stent and delivery system	PASS
Radiopacity	To evaluate the radiopaque marker visibility during and after device delivery	PASS
Catheter material	To verify catheter material requirements	PASS
Hydrophilic coating voids	To evaluate the durability of the hydrophilic coating	PASS
Guide catheter compatibility	To measure the catheter outer diameter (OD) to ensure compatibility with 6 F guide catheter	PASS
Catheter working length	To measure the length of the delivery catheter	PASS
Sharp edges	To ensure the outer surface of the delivery catheter is free from sharp edges	PASS
Tapered tip	To measure the tip length and tip flat and ensure tip is long/tapered enough to navigate through the vasculature	PASS
Proximal catheter length	To measure the proximal catheter inner diameter (ID) and length	PASS
Guidewire compatibility	To evaluate the rapid exchange lumen ID compatibility with guidewire	PASS

Test	Method	Results / Conclusions
Rapid exchange port surface	To ensure the rapid exchange port surface is smooth	PASS
Luer compatibility and catheter flushing	To evaluate the ability to flush the guidewire lumen	PASS
Rapid exchange lumen flushing	To evaluate the ability to flush the rapid exchange lumen	PASS
Tracking force	To measure the force during tracking of the delivery catheter through the vasculature	PASS
Deployment resistance force	To evaluate the ability of the catheter to resist stent deployment when the valve is tightened on the inner catheter	PASS
Deployment force	To measure the force required to deploy the stent	PASS
Catheter removal	To evaluate the ability of the catheter to be removed without dislodging the stent	PASS
Catheter kink radius/resistance	To evaluate the flexibility and kink of the delivery catheter	PASS
Deployed stent vessel conformity	To evaluate the ability of the stent to conform to the vessel	PASS
Deployed stent compatibility with other devices	To evaluate compatibility of the stent with procedure accessories including 2.7 F microcatheter and 0.014" guidewire	PASS
Tensile strength	To evaluate the tensile strength of the catheter joints	PASS
Torque resistance	To evaluate the torque strength of the delivery catheter	PASS
Venous leak pressure	To evaluate the delivery system for leakage	PASS
Catheter corrosion resistance	To evaluate the resistance of the delivery catheter to corrosion	PASS

Biocompatibility

The River Stent is a permanent implant in direct contact with circulating blood. The River Stent System (delivery system) is an externally communicating device in direct contact with circulating blood with a limited duration of contact of ≤ 24 hours. All patient contacting components of the River Stent System were tested to

evaluate the materials for biocompatibility and toxicity in accordance with ISO 10993-1 and the FDA guidance document, “Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process".” **Table 4** and **Table 5** summarize the biocompatibility tests conducted for the River Stent System.

Table 4: Biocompatibility Testing of the River Stent

Test	Method	Results / Conclusions
Cytotoxicity	Minimum Essential Medium (MEM) Elution Assay with L-929 Cells (ISO 10993-5)	Non-cytotoxic
Sensitization	Guinea Pig Maximization Test (ISO 10993-10)	Non-sensitizing
Intracutaneous Reactivity	Intracutaneous Reactivity Test (ISO10993-10)	Non-irritating
Acute Systemic Toxicity	Acute Systemic Injection Test (ISO 10993-11)	Non-toxic
Material-mediated Pyrogenicity	Rabbit Pyrogen Test (Material Mediated) (ISO 10993-11)	Non-pyrogenic
Subchronic Toxicity	Chemical Characterization and Toxicological Risk Assessment (TRA)	Non-toxic
Chronic Toxicity	Chemical Characterization and TRA	Non-toxic
Genotoxicity	Chemical Characterization and TRA	No genotoxic concern identified
Carcinogenicity	Chemical Characterization and TRA	No carcinogenic concern identified
Implantation	180-Day Good Laboratory Practice (GLP) Canine Study	Acceptable local tissue response
Hemocompatibility	ASTM Hemolysis Assay - Direct Contact and Extract Method (ASTM F756/ISO 10993-4)	Non-hemolytic
	SC5b-9 Complement Activation Assay (ISO 10993-4)	Not an activator of the complement system
	Partial Thromboplastin Time (PTT) – Direct Contact (ISO 10993-4/ASTM F2382)	Does not have effect on coagulation compared to controls

Test	Method	Results / Conclusions
	Non-Anticoagulated Venous Implant (NAVI) 4-Hour Canine Thrombogenicity Test (ISO 10993-4)	Non-thrombogenic

Table 5: Biocompatibility Testing of the River Stent System (Delivery System)

Test	Method	Results / Conclusions
Cytotoxicity	MEM Elution Assay with L-929 Cells (ISO 10993-5)	Non-cytotoxic
Sensitization	Guinea Pig Maximization Test (ISO 10993-10)	Non-sensitizing
Intracutaneous Reactivity	Intracutaneous Reactivity Test (ISO10993-10)	Non-irritating
Acute Systemic Toxicity	Acute Systemic Injection Test (ISO 10993-11)	Non-toxic
Material-mediated Pyrogenicity	Rabbit Pyrogen Test (Material Mediated) (ISO 10993-11)	Non-pyrogenic
Hemocompatibility	ASTM Hemolysis Assay - Direct Contact and Extract Method (ASTM F756/ISO 10993-4)	Non-hemolytic
	SC5b-9 Complement Activation Assay (ISO 10993-4)	Not an activator of the complement system
	PTT – Direct Contact (ISO 10993-4/ASTM F2382)	Does not have effect on coagulation compared to controls
	NAVI 4-Hour Canine Thrombogenicity Test (ISO 10993-4)	Non-thrombogenic

Shelf-Life Testing

River Stent System test samples were subjected to accelerated aging for 18 months in addition to sterilization and distribution conditioning. The devices were tested for compliance to the device specifications including package integrity, product visual inspection, product dimensional testing, austenite finish temperature, radial force, corrosion resistance, simulated use, tensile testing, torque strength, tracking and deployment forces, kink resistance, venous leak pressure, coating integrity, and particulate testing. All test samples met the acceptance criteria supporting an 18-month shelf-life for the River Stent System.

Sterilization

The River Stent System is sterilized using ethylene oxide (EO). The sterilization cycle was validated to a sterility assurance level (SAL) of 10^{-6} per ISO 11135:2014, "Sterilization of health-care products – Ethylene oxide – Requirements for the development, validation and routine control of a sterilization process for medical devices." EO and ethylene chlorohydrin (ECH) residuals met the requirements of ISO 10993-7:2008, "Biological evaluation of medical devices – Part 7: Ethylene oxide sterilization residuals." The River Stent System was tested for bacterial endotoxins and met the specified endotoxin specification of < 2.15 endotoxin units per device for devices with potential contact with CSF.

B. Animal Studies

Objectives. The objectives of the animal study were to test the safety and performance of the River Stent System in a canine venous sinus implantation model.

Methods: A GLP animal study was conducted to evaluate the safety and performance of the River Stent System in a canine venous sinus implantation model. The implantation procedure was evaluated by two experienced interventionalists and included assessing the ease of insertion into guide catheter, tracking over a guidewire, and deployment; marker band radiopacity before and during stent deployment, and of the implanted stent. Animals were then distributed into three termination time points: 28-day, 90-day, and 180-day. Angiograms were obtained before and after stent deployment during the implant procedure and at termination. After termination, animals were evaluated via gross complete necropsy and tissues were collected for histopathological evaluation. Study endpoints included overall animal health, device performance, and long-term vascular response to the implant.

Results: Performance and handling measures during the implantation procedure were all rated acceptable or excellent. All animals remained generally healthy throughout the duration of the study and no significant excursions in clinical pathology values were noted.

No relevant gross abnormalities were observed in the organs examined at necropsy for any animal at any time point. Histopathology showed no evidence of luminal thrombus, loss of endothelial coverage or wall integrity, hemorrhage, necrosis or abnormal mineralization in the implanted vessels. The inflammatory response to the stents consisted of resident macrophages and minimal (mostly absent) multinucleated giant cells, which tended to decrease with time. Survey organ findings were minimal to mild in severity and interpreted to be incidental background changes with no adverse effects indicative of systemic toxicity.

Histomorphometry showed minimal lumen reduction in the sinus section of the implanted vessels which remained consistent and stable from day 28 to day 180.

Conclusions: The results of the animal studies showed satisfactory safety and performance of the River Stent System.

X. SUMMARY OF CLINICAL INFORMATION

Serenity Medical, Inc. performed a clinical study, "Clinical Evaluation of the Serenity River Stent System to Treat Idiopathic Intracranial Hypertension - The River Trial," to support the safety and probable benefit of the River Stent System as a treatment for stenting of venous sinus stenosis in patients with IIH that have failed medical therapy. "The River Trial" was conducted in the United States (U.S.) under Investigational Device Exemption (IDE) G180008. Data from this study was the basis for the HDE approval. A summary of the clinical study is presented below.

An imaging core laboratory was used for evaluation of venous sinus stenosis for the primary probable benefit endpoint analysis. A combined Clinical Events Committee-Data Monitoring Committee (CEC-DMC) provided safety oversight and adjudicated adverse events.

A. Study Design

Patients were treated between August 24, 2018, and September 20, 2021. "The River Trial" was a prospective, non-randomized, single-arm, multi-center, observational study with 1-year follow-up. A total of 39 subjects were treated from five U.S. institutions.

B. Study Selection Criteria

Enrollment in "The River Trial" was limited to patients who met all of the following inclusion criteria:

- Subject is > 18 years old and has given informed consent.
- Diagnosis of IIH per modified Dandy criteria.
- CSF opening pressure is > 25 cm H_2O.
- Radiological examination (magnetic resonance venography (MRV) or computed tomographic venography (CTV)) or retrograde catheter venography (RCV) shows bilateral transverse-sigmoid venous sinus stenosis (> 50%) or unilateral stenosis of the dominant sinus with contralateral hypoplastic sinus and no stenosis of the superior sagittal sinus.
- Presence of IIH clinical symptoms:
    - Headaches: Score > 59 (severe impact) on the HIT-6 scale, refractory to medical therapy (e.g., acetazolamide 1000 mg BID (bis in die; twice

daily), topiramate 100 mg BID, or other headache medication), or medication intolerance for ≥ 4 weeks;

OR

- Visual field loss: Defined by perimetric mean deviation (PMD) between -6 decibels (dB) and -30 dB in one or both eyes (with papilledema Frisén grade > 1) despite at least 2 weeks of medical therapy with acetazolamide reaching 1000 mg BID, or if the visual deteriorates by more than 2 dB during treatment, or treatment intolerance.
  Note that if only one eye fulfills criteria for visual field loss, and only one eye has grade 2 or higher papilledema, then they must be the same eye. This is to prevent the inclusion of a patient where one eye has severe visual field loss with atrophy (with no chance of improvement) and the other has papilledema but only mild visual field loss.

- In the absence of this study, the subject would have been offered a surgical intervention by ONSF, CSF shunting procedure, or venous sinus stenting with an off-label device.

Angiographic Inclusion Criteria

- Catheter manometry shows a pressure gradient > 8 mmHg across the transverse sigmoid sinus stenosis.
- Venographic evidence of sinus stenosis (> 50%).

Patients were <u>not</u> eligible to enroll in "The River Trial" if they met any of the following exclusion criteria:

- Subject presenting with de novo papilledema and severe visual field (VF) deficit (VF loss ≥ 15 dB) that requires immediate surgical treatment without prior attempt of medical therapy.
- Subject has no measurable visual acuity at one meter in the study eye.
- Currently has or plans to have an implanted CSF shunt.
- History of previously implanted intra-cranial sinus stent.
- Transverse-sigmoid sinus vessel size < 5 mm or > 10 mm.
- Creatinine > 1.5 mg/dl and/or creatinine clearance < 60 mL/min (except if patients are already on hemodialysis).
- Allergic to imaging contrast media (iodine or gadolinium) despite premedication.
- Allergic to nitinol or nickel.
- Contra-indication to general anesthesia.
- Contra-indication to aspirin, clopidogrel or other anticoagulant.

- Hypercoagulable state (Factor V Leiden, protein C or S deficiency, anticardiolipin antibodies, Lupus anticoagulant, B2-glycoprotein-1 antibodies, or hyperhomocysteinemia).
- Currently requiring full anti-coagulation for other medical reasons, such as atrial fibrillation (AF), artificial cardiac valves, deep vein thrombosis, pulmonary embolism, etc.
- History of stroke or transient ischemic attack (TIA).
- History of AF or other risks of stroke.
- History of deep vein thrombosis or pulmonary embolism.
- History of severe chronic obstructive pulmonary disease (COPD) or other severe respiratory disease.
- History of severe carotid atherosclerotic disease.
- History of heart failure, dilated cardiomyopathy, or congenital heart conditions, etc. that are at high thrombogenic risk.
- History of uncontrolled diabetes.
- Use of tetracycline derivative, retinoid, or vitamin A during the last 3 months except topical applications which are allowed.
- Cerebral vascular lesions (arteriovenous malformation (AVM), arteriovenous fistula, aneurysms, significant stenosis of extra- or intra-cranial vessels other than the targeted venous sinus stenosis, intracranial artery dissection, etc.).
- Patient has vision loss due to other disease (e.g., cataract, macular degeneration, glaucoma, etc.).
- Inability to provide reliable and reproducible visual field examinations (> 15% false positive errors and/or failure to maintain fixation for eye monitoring).
- For female subject of childbearing potential, pregnant or not willing to use contraceptive for 12 months.
- Presence of a physical, mental or social condition that could prevent adequate one-year follow-up (homelessness, drug dependency, anticipation of moving far away, life threatening disease, terminal illness).
- Anatomical anomaly of the venous sinus which would prevent safe catheterization and stenting (e.g., multi-channel sinus).
- Currently enrolled in a premarket investigational study. Enrollment in a post market study that does not impact the River Stent procedure or device is allowed.

C. **Follow-Up Schedule**

Subjects in "The River Trial" were evaluated post-index procedure before discharge, 1 week to 1 month, 3 months, 6 months, and 12 months post-procedure and annually through 5 years.

Baseline and follow-up clinical assessments included:

- Physical exam

- Laboratory assessments
- Neuro-ophthalmological assessments
- Headache Impact Test (HIT-6)
- Tinnitus Functional Index (TFI)
- Quality of life assessments: Short-Form (SF)-12, National Eye Institute Visual Function Questionnaire (NEI-VFQ)-25 with neuro-ophthalmology supplement, EQ-5D

Adverse events were recorded at all follow-up visits.

D. **Clinical Endpoints**

Primary Safety Endpoint: The primary safety endpoint of "The River Trial" is major adverse event (MAE) rate at 12 months post River Stent procedure. The MAE is a composite of the following:

- Moderate or severe stroke [National Institutes of Health Stroke Scale (NIHSS) > 3]
- Neurological death
- Perforation of sinus or cerebral vein
- Thrombosis of sinus or cerebral vein
- Device distal embolization
- Need for target vessel revascularization or need for IIH alternate procedure (new venous sinus stenting, CSF shunting or ONSF)

The 12-month MAE rate was evaluated against a performance goal of 51.7% based on standard of care CSF shunting procedures derived from the published literature.

Primary Probable Benefit Endpoint: The primary probable benefit endpoint is a composite at 12 months of the following:

A. Absence of significant (> 50%) stenosis of the stented sinus and of new significant (> 50%) stenosis of the other cerebral venous sinuses on retrograde catheter venography (RCV).

AND

B. Decrease of trans-stent pressure gradient (difference between the pressure measured in the torcula, proximal to the stent, and the pressure measure in the sigmoid sinus, proximal to the stent) to less than 8 mmHg.

AND

C. Clinically relevant improvement in the main clinical outcome per specific inclusion criteria and stabilization or better of the other:

- Headaches: Improvement in the HIT-6 scale by ≥ 5 points and improvement or stabilization of visual field.
  OR
- Ophthalmic: Improvement in visual field by ≥ 30% of the baseline value in the study eye (or at least one eye, with stabilization or better of the other eye, if a subject has 2 study eyes) and improvement or stabilization of headaches.

  Note: If the subject fulfills both the headache and the ophthalmic criteria to enter the trial, it will be analyzed in the ophthalmic group for the purpose of the primary probable benefit endpoint.

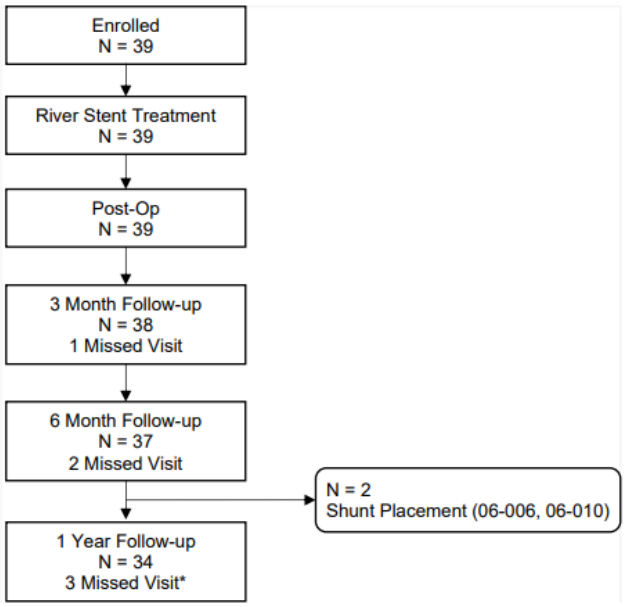
The primary probable benefit endpoint was evaluated descriptively.

Secondary Endpoints: Secondary endpoints were evaluated descriptively and included the following measures:

- Individual components of MAE at 12 months.
- CSF opening pressure at 12 months.
- Stent patency at 12 months.
- Neuro-ophthalmological outcomes at 12 months.
- Medications at 12 months.
- Procedure parameters.
- New venous sinus stenosis at 12 months.

E. **Subject Accountability:**

Subject accountability is shown in **Figure 3** and **Table 6**. A total of 39 subjects were enrolled and treated in the study and 34 completed the 1-year visit. Two subjects exited the study early, prior to 1 year, with both subjects undergoing a CSF shunt procedure at 6 months. Three subjects missed the 1-year visit. Of the 34 subjects who completed the 1-year visit, 8 subjects did not undergo the RCV and manometry (RCVM) assessment necessary to assess the primary probable benefit endpoint. In total, 22 subjects met all the selection criteria and had all the elements for calculation of the primary probable benefit endpoint including RCVM, HIT-6, reliable visual fields, and known primary probable benefit events. As of the database cut-off date, four additional subjects exited the study after the 1-year visit due to loss to follow-up.



*One subject missed the 1-year visit but was followed by the site for major adverse events via phone and therefore was included in the primary safety endpoint analysis.

Figure 3: Subject Accountability

All primary safety and probable benefit analyses were performed using the modified intent-to-treat (mITT) data set which included all enrolled subjects who had the River Stent System attempted (device introduced in the vasculature). Because all enrolled subjects had the device implant attempted, the mITT population consists of all enrolled subjects.

Table 6: Subject Accounting by Follow-Up Visit and Endpoints

Characteristic	Number of Subjects
mITT	39
River Stent attempted	39
River Stent implanted	39
Follow-Up Visits Completed	
3-month visit	38
6-month visit	37
1-year visit	34
Primary Safety Endpoint[1]	37
Subjects with 1-year visit completed	34
Subjects with alternate IIH surgical procedure (CSF shunt) at 6-months due to recurrent IIH symptoms	2
Subject who missed 1-year visit but was contacted by phone by study site for major adverse event data collection for primary safety	1

Characteristic	Number of Subjects
Primary Probable Benefit Endpoint[2]	22
Met all inclusion criteria and had all the elements for calculation of the primary probable benefit endpoint, including RCVM, HIT-6, and reliable visual fields	20
Withdrew at 6-months due to alternate IIH surgical procedure (CSF shunt placement)	2
Missing Data for Elements of Primary Probable Benefit Endpoint at 1-Year	17
Missed 1-year visit (lost to follow-up)	3
Missing RCVM (at 1-year)[3]	12
Missing HIT-6[4]	2
Missing visual field data[4, 5]	4
Unreliable visual field data[5]	5
Did not meet headache or visual field eligibility criteria	1
Subjects with Data for Key Secondary Endpoints at 1-Year	
CSF opening pressure[2]	22
Stent patency	26
Headache (HIT-6)	34
Papilledema (Frisén grade)	32

[1]37 subjects contributed to the primary safety endpoint, 3 of which did not complete the 1-year visit but had confirmed primary safety events.
[2]Four out of 20 subjects with primary probable benefit endpoint data available at 1-year did not have 1-year CSF opening pressure data.
[3]This includes: 3 lost to follow-up, 7 refused the procedure, 2 with CSF shunt who reached primary safety endpoint and were not offered the procedure.
[4]CSF shunt subjects did not collect 1-year probable benefit endpoint data.
[5]One subject with missing visual field data and one subject with unreliable visual field data also was missing RCVM at 1-year.

F. **Demographic Data**

Demographics and baseline characteristics of "The River Trial" patients are summarized in **Table 7** below. The cohort was mostly female (38/39) with an average age of 35 years and an average body mass index of 35.4 kg/m^2. There were 34 subjects enrolled based on headache criteria, 4 based on visual criteria, and one subject who did not meet headache or visual eligibility criteria at study entry (refer to **Table 8** below).

Fourteen (14) of the 39 subjects enrolled had a history of papilledema but no baseline papilledema in either eye. Twenty-five (25) of the 39 subjects enrolled had some degree of papilledema (Frisén grade ≥ 1) at baseline in at least one eye.

Fourteen (14) subjects had papilledema Frisén grade 1 in the worst eye, 11 had papilledema Frisén grade 2 and 2 subjects had papilledema Frisén grade 3 in the worst eyes. All 4 of the 4 subjects enrolled based on visual criteria had Frisén grade 2 in both eyes. Of the 34 subjects enrolled based on headache criteria, 14 had no baseline papilledema, 14 had Frisén grade 1 at baseline and 6 had Frisén grade > 1 at baseline. The one subject who did not meet headache or visual eligibility criteria had papilledema with Frisén grade 3 in one eye and grade 2 in the other. See **Table 9** below.

Table 7: Subject Demographics and Baseline Characteristics [mITT]

Characteristic	Value
Age at Enrollment (Years)	
Mean ± Standard Deviation [SD] (N)	35.7 ± 12.01 (39)
Median	31.0
Min, Max	19, 65
Female Gender, n/N (%)	38/39 (97.4%)
Race / Ethnic Origin, n/N (%)[1]	
Asian	2/39 (5.1%)
Black or African Origin	8/39 (20.5%)
Caucasian	24/39 (61.5%)
Hispanic or Latino	8/39 (20.5%)
Native American or Alaskan Native	1/39 (2.6%)
Other	4/39 (10.3%)
Body Mass Index (kg/m^2)	
Mean ± SD (N)	35.42 ± 7.975 (39)
Median	34.00
Min, Max	20.0, 56.5
Study Enrollment by Symptoms, n/N (%)	
Headache Group (HIT-6 score > 59)	34/39 (87.2%)
Ophthalmic Group (PMD: -6 dB to -30 dB)	4/39 (10.3%)
No Symptom Group	1/39 (2.6%)
Study Eye, n/N (%) (Ophthalmic Group Only)	
Right	0/4 (0.0%)
Left	2/4 (50.0%)
Both	2/4 (50.0%)

[1]Some subjects reported more than one race / ethnic origin.

Table 8: Enrollment by Criteria [mITT]

	Headache Criteria (HIT-6 score > 59)	
Ophthalmic Criteria (PMD: -6 dB to -30 dB)	**Headache Present n/N (%)**	**Headache Absent n/N (%)**
Ophthalmic Present n/N (%)	4/39 (10.3%)[1]	0/39 (0.0%)
Ophthalmic Absent n/N (%)	34/39 (87.2%)[2]	1/39 (2.6%)[3]

[1]4/4 subjects enrolled based upon ophthalmic criteria had bilateral papilledema Frisén grade 2 at baseline.

[2] 6/34 subjects enrolled based upon headache criteria had papilledema with Frisén grade > 1 at baseline and 14/34 subjects had papilledema with Frisén grade = 1 at baseline.

[3]One subject did not qualify for the study based on inclusion 5 requiring the presence of IIH clinical symptoms with specified criteria for headache or visual field loss. This subject had bilateral papilledema (Frisén grade 2 in one eye and Frisén grade 3 in the other eye) at baseline.

Table 9: Papilledema at Baseline

	Frisén > 1	**Frisén = 1**	**Frisén = 0**	**Total**
Headaches group	6	14	14	**34**
Visual field defect group	4	0	0	**4**
No group	1	0	0	**1**
Total	**11**	**14**	**14**	

Subjects received pre- and post-procedure antiplatelet therapy in the form of aspirin and clopidogrel. All enrolled subjects underwent successful stent placement procedures. The average time from device insertion to catheter removal was 21.8 minutes. Intra-procedural sinus stenosis and pressure measurements are summarized in **Table 10**.

Table 10: Intraprocedural Venous Sinus Stenosis and Pressure Measurements

Venous Sinus Measurement	**Mean ± SD (n)**
Stenosis Measurements (Before Stenting)	
Downstream diameter (mm)	7.42 ± 1.126 (39)
Upstream diameter (mm)	7.46 ± 1.715 (39)
Stenotic diameter (mm)	3.77 ± 6.541 (39)
Length of stenosis (mm)	19.86 ± 11.743 (38)
Trans-stenotic Pressure Gradient (mmHg)	
Pre-stenting	16.1 ± 10.82 (35)
Post-stenting	1.7 ± 1.58 (39)
Percent Stenosis (%)[1]	
Pre-stenting	61.6 ± 6.77 (39)
Post-stenting	24.9 ± 11.83 (39)
[1]Per core lab evaluation.	

G. Clinical Data Analysis and Results

Primary Safety Analysis:
The primary safety endpoint was the MAE rate at 12 months post River Stent procedure compared to a pre-specified performance goal of 51.7%. The MAE rate at 1 year was 5.4% (2/37) [95% confidence interval: (0.7%, 18.2%)] with 2 subjects requiring a shunt placement after the 6-month visit (**Table 11**). The upper 95% confidence limit is lower than the pre-specified performance goal; therefore, the primary safety endpoint was met ($p < 0.0001$, one-sided exact binomial test). This analysis was performed on the mITT population and included one subject who missed the 1-year visit but was followed by the site for primary safety endpoint data (two subjects who missed the 1-year follow-up visit were excluded from the analysis below). As a worst-case analysis, subjects who missed the 1-year visit were counted as experiencing an MAE. The upper 95% confidence limit for the worst-case analysis was lower than the performance goal.

Table 11: Primary Safety Endpoint – MAE Rate at 1 Year

Primary Safety Endpoint	Subjects with events % (n/N)	95% CI [LCL, UCL][2]	Performance Goal	p-value[1]
Total MAE rate	5.4% (2/37)	0.7%, 18.2%	51.7%	< 0.0001 (met)
Worst-case MAE rate (subjects with missing data counted as having MAE)	10.3% (4/39)	2.9%, 24.2%	--	--

[1]One-sample exact binomial test.
[2]Confidence Interval (CI), Lower Confidence Limit (LCL), Upper Confidence Limit (UCL).

Adverse Events Summary
A total of 110 adverse events (AEs) were reported in 33 subjects, including 9 serious adverse events (SAEs). No unanticipated adverse device effects (UADEs) or deaths occurred. Serious adverse event rates by the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term are shown in **Table 12**.

Table 12: Serious Adverse Events

System Organ Class Preferred Term	Subjects, n (%) N=39	Events	Related to Device	Related to Procedure	Resolved
Nervous system disorders	**2 (5.1%)**	**3**	**1**	**1**	**2**
Idiopathic intracranial hypertension[1]	2 (5.1%)	3	1	1	2
Infections and infestations	**2 (5.1%)**	**2**	**0**	**0**	**2**
Bacteremia	1 (2.6%)	1	0	0	1
Corona virus infection	1 (2.6%)	1	0	0	1
Vascular disorders	**2 (5.1%)**	**2**	**0**	**0**	**2**
Vascular stenosis	1 (2.6%)	1	0	0	1
Vein dissection	1 (2.6%)	1	0	0	1
Gastrointestinal disorders	**1 (2.6%)**	**1**	**0**	**1**	**1**
Gastrointestinal hemorrhage	1 (2.6%)	1	0	1	1
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**1 (2.6%)**	**1**	**0**	**0**	**0**
Plasma cell myeloma	1 (2.6%)	1	0	0	0

[1]One event of IIH was classified as both device and procedure related.

A total of 10 subjects experienced 14 adverse events classified as definitely or probably (likely) related to the study device and/or procedure, including 2 SAEs (**Table 13**). The most common device/procedure related adverse event was headache (10.3%), with all other events occurring in 1 or 2 subjects.

Table 13: Device / Procedure Related Adverse Events

System Organ Class Preferred Term	Subjects n (%) N=39	Number of Events	Related to Device	Related to Procedure
Nervous system disorders				
Headache[1]	4 (10.3%)	4	2	4
Idiopathic intracranial hypertension[1]	1 (2.6%)	1	1	1
Paresthesia	1 (2.6%)	1	0	1

System Organ Class Preferred Term	Subjects n (%) N=39	Number of Events	Related to Device	Related to Procedure
Injury, poisoning and procedural complications				
Contusion	2 (5.1%)	2	0	2
Respiratory, thoracic and mediastinal disorders				
Epistaxis	2 (5.1%)	2	0	2
Hemoptysis	1 (2.6%)	1	0	1
Eye disorders				
Eye pain	1 (2.6%)	1	0	1
Gastrointestinal disorders				
Gastrointestinal hemorrhage	1 (2.6%)	1	0	1
Musculoskeletal and connective tissue disorders				
Pain in extremity	1 (2.6%)	1	0	1

[1]Two headache events and one IIH event were classified as both device and procedure related.

Primary Probable Benefit Analysis

The primary probable benefit endpoint was defined as the proportion of subjects experiencing a composite measure of success based on venography, manometry, and clinical outcomes through 12 months post-procedure as defined above.

Assessment of stenosis was based on findings from an independent imaging core laboratory. A total of 27 subjects had RCVM at 1 year. Twenty-two (22) of 39 subjects (56.4%) treated with the River Stent had data available at the 1-year visit for all elements of the primary probable benefit outcome or known primary endpoint events. For the 27 subjects with RCVM data at 1-year, one subject had missing visual field data, four subjects had unreliable visual field data, and one subject did not meet headache or visual field eligibility criteria for study enrollment, resulting in 22 subjects with all elements of the primary probable benefit endpoint for analysis. Two subjects withdrew at 6-months due to alternate IIH surgical procedure (CSF shunt placement), and these subjects were included in the analysis population of the primary probable benefit endpoint. For these 22 subjects with data available for all elements of the primary probable benefit outcome and known primary endpoint events (treatment with CSF shunting), results show that 54.5% (12/22) of subjects met all components of the primary probable benefit endpoint (**Table 14**). A sensitivity analysis utilizing multiple imputation was performed to evaluate the impact of missing data (**Table 14**). Results of this analysis were consistent with the primary results. The sponsor conducted a worst-case analysis for the primary

probable benefit endpoint by imputing missing data as failures which resulted in 30.8% (12/39) subjects meeting the primary probable benefit endpoint.

The sponsor evaluated the individual components of the primary probable benefit endpoint as shown in **Table 15**. Of the 20 subjects with 1-year follow-up visits with all elements to calculate the primary probable benefit endpoint, 4 subjects did not have 1-year CSF opening pressure data to evaluate effects on intracranial pressure.

Table 14: Primary Probable Benefit Endpoint at 1 Year

Primary Probable Benefit Endpoint	Subjects % (n/N)	95% CI [LCL, UCL]
Pre-specified Endpoint		
mITT with observed reliable visual field data and all elements to calculate probable benefit endpoint	54.5% (12/22)	32.2%, 75.6%
Additional Analyses for Sensitivity of Primary Probable Benefit Analysis		
mITT with multiple imputation (missing at random assumption)	55.4%	38.6%, 71.9%
mITT, all 39 subjects implanted with River Stent, missing data imputed as failure (worst-case analysis)	30.8% (12/39)	17.0%, 47.6%

Table 15: Individual Components of Primary Probable Benefit Endpoint

Primary Probable Benefit Endpoint Component	Subjects, % (n/N)
Absence of significant (> 50%) stenosis on RCV	**88.9% (24/27)**
Of the stented sinus	100.0% (27/27)
Of new significant > 50% stenosis of other cerebral venous sinuses	88.9% (24/27)
Decrease of trans-stent pressure gradient < 8 mmHg	**88.9% (24/27)**
Clinically relevant improvement	**73.1% (19/26)**
Headaches: improvement in HIT-6 by 5 points and improvement or stabilization of visual field	76.0% (19/25)
Ophthalmic: improvement in visual field by 30% in the study eye and improvement or stabilization of headaches	0.0% (0/1)

Note: Component-level results are presented based on data availability. Of 39 subjects, 3 missed the 1-year visit and 2 withdrew at 6 months due to alternative IIH treatment (CSF shunt), resulting in 34 subjects eligible across components. For components 1 and 2, 7 additional subjects lacked RCV assessments (n=27). For component 3, 8 additional subjects had missing or unreliable visual field data (n=26).

Secondary Endpoints

New Venous Sinus Stenosis

There were 27 subjects who had RCVM at 1 year out of the 39 subjects enrolled and treated. Per core lab evaluation of the images, new venous sinus stenosis was reported in 11.1% (3/27) of subjects at 1 year, including one new stenosis of the transverse sinus and two superior sagittal sinus stenosis; all 3 stenoses were adjacent to the torcula. One additional subject had a shunt placed after 6 months for a new venous sinus stenosis in the superior sagittal sinus for a total new venous sinus stenosis rate of 14.3% (4/28). There was no in-stent stenosis observed in the cohort.

CSF Opening Pressure, Neuro-ophthalmology Evaluations, and Quality of Life

Results for CSF opening pressure, headache (HIT-6), and papilledema (Frisén grade) are summarized in **Table 16** for the mITT cohort with assessments completed for these secondary outcomes. Additional secondary outcome data collected in "The River Trial" are summarized in the labeling. Three subjects in the ophthalmic group, 30 subjects in the headache group, and one subject in the 'no symptom' group completed the 1-year visit. Only 22 of 39 subjects enrolled and treated in the study had CSF opening pressure measurements at the 1-year visit and 4 of 22 (18%) subjects reported CSF opening pressures > 25 cm H_2O at the 1-year visit.

Table 16: Summary of Secondary Outcomes

Variable	Baseline (BL)	3 Month	6 Month	1 Year	Change (1 Year – BL)
CSF Opening Pressure (cm H_2O)	32.9 ± 6.92 (39)	NA	NA	15.7 ± 7.40 (22)	-33.5 ± 36.36 (22)
HIT-6	69.5 ± 6.12 (39)	58.4 ± 11.84 (36)	56.5 ± 10.55 (37)	56.5 ± 10.49 (34)	-12.9 ± 9.57 (34)
Frisén Grade[1]	0.9 ± 0.81 (78)	0.1 ± 0.39 (76)	0.0 ± 0.20 (74)	0.0 ± 0.28 (64)	NR

NA – Not applicable.
NR – Not reported.
Mean ± standard deviation (n) shown.
[1]n for this measure indicates number of eyes.

Medication Usage

The average daily medication dose for acetazolamide and topiramate decreased at 1 year as compared to baseline (**Table 17**). Of the subjects taking the medication at baseline who had information on IIH medication usage at 1 year, 47% (8/17) and 29% (2/7) stopped taking acetazolamide and topiramate, respectively, by 1 year.

Table 17: Medication Daily Dose (mg/day)

IIH Medication	Baseline (BL) N=39	1 Year N=34	Change (1 Year – BL) N=24
Acetazolamide	986.8 ± 658.67 (19)	513.9 ± 609.20 (18)	-529.4 ± 565.15 (17)
Topiramate	97.2 ± 63.05 (9)	66.7 ± 48.41 (9)	-32.1 ± 87.46 (7)
Furosemide	30.0 ± 14.14 (2)	30.0 ± 14.14 (2)	0.0 ± 0.00 (2)
Note: IIH medication usage for each visit was determined based on the start and end dates for the medication usage. Daily dose is the mg/day based on the dose at each visit.			

Additional Analyses: Long-Term Follow-Up

The sponsor collected long-term follow-up data, including both clinical assessments and contrast-enhanced magnetic resonance venography (CE-MRV), through five years post-implantation to evaluate the durability of treatment effects. Subjects in the study were reconsented for long-term follow-up assessments after the 1-year visits had been completed.

A total of 21 subjects underwent a CE-MRV between 3 and 5 years post-implantation (**Table 18**) and data from these patients were pooled to assess the long-term probable benefit.

Table 18: Timing of Long-Term CE-MRV

Variable	Number of Subjects (n= 21)
Year 3 to Year 4	4/21 (19.0%)
Year 4 to Year 5	9/21 (42.9%)
After Year 5	8/21 (38.1%)

Data available at 1 year and for long-term follow-up were not derived from the same subjects due to missingness at these time points. The sponsor calculated a post-hoc long-term probable benefit endpoint defined as a composite of the following endpoints at the time of the long-term CE-MRV (i.e., 3-5 years and varying across subjects):

I. Clinically relevant improvement in headache defined as ≥ 5-point reduction in HIT-6;
and
II. Improvement or stable absence of papilledema;
and

III. Absence of significant (> 50%) stenosis of the stented sinus and of new significant (> 50%) stenosis of the other cerebral venous sinuses on CE-MRV.

As shown in **Table 19**, among the 21 mITT subjects with long-term CE-MRV data, 85.71% (18/21) met the long-term probable benefit endpoint. Eighteen (18) of 21 subjects demonstrated sustained improvement in headache symptoms and 21 of 21 subjects demonstrated resolution or stabilization of papilledema compared to their baseline. Additionally, 100% (21/21) showed no evidence of significant venous sinus stenosis at the time of follow-up imaging.

Table 19: Long-Term Probable Benefit Endpoint

Long-Term Probable Benefit Endpoint	**Subjects % (n/N)**	**95% CI (LCL, UCL)**
mITT	**85.71% (18/21)**	**(63.66, 96.95)**
Improvement in HIT-6 by ≥ 5points	85.71% (18/21)	N/A
Improvement or stable absence of papilledema	100% (21/21)	N/A
Absence of significant (> 50%) stenosis on MRV	100% (21/21)	N/A

Long-Term New Venous Sinus Stenosis:
Two patients were found to have new stenoses at the time of their long-term CE-MRV follow-up. One patient developed a progression from mild to moderate stenosis in the contralateral transverse sinus, which remained asymptomatic. The other patient developed two new severe stenoses, one above the stent (end-stent stenosis) and one in the superior sagittal sinus, both of which were symptomatic (recurrence of headaches and transient visual obscuration (TVO) but not papilledema). These stenoses were graded by the core lab as < 50% stenosis.

Long-Term Clinical Endpoints:
Additional long-term clinical data were collected using the same metrics assessed at the 1-year follow-up and are presented in **Table 20** for headache and papilledema assessments. Headache impact scores (HIT-6) consistently improved by approximately 12 points from baseline across the 2- to 5-year follow-up periods. Frisén grade showed generally stable or improved values over time, supporting ongoing symptom resolution in patients with papilledema.

Additional secondary endpoints (visual function measures, including Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity, visual field mean deviation (PMD), and retinal nerve fiber layer (RNFL) thickness, diplopia, TVOs, EQ-5D visual analogue scale (VAS) scores, TFI) are summarized in the labeling.

Table 20: Summary of Long-Term Clinical Outcomes

Variable	Baseline (BL)	2 Year – BL Change	3 Year – BL Change	4 Year – BL Change	5 Year – BL Change
HIT-6[1]	69.5 ± 6.1 (39)	-12.2 ± 10.5 (26)	-12.4 ± 9.7 (25)	-12.7 ± 9.0 (21)	-12.4 ± 9.0 (10)
Frisén Grade[2,3]	0.9 ± 0.81 (78)	0.0 ± 0.21 (46)	0.0 ± 0.14 (48)	0.0 ± 0.00 (38)	0.0 ± 0.00 (16)

Mean ± standard deviation (n).
[1]Measured across full population (i.e., both headache and ophthalmic group).
[2] n for this measure indicates number of eyes.
[3]Measured at single time points (i.e., 2 years, 3 years, 4 years, 5 years) as opposed to change from baseline.

Weight-Loss Data

To better understand weight management efforts among participants with obesity (BMI ≥ 30), additional self-reported data were collected on prior and ongoing weight loss attempts (**Table 21**). Most subjects reported active or previous efforts, including lifestyle changes, GLP-1 receptor agonist use (n=5), and bariatric surgery (n=4), both before and after stenting.

The majority of subjects reported pursuing weight loss both before (84.6%) and after treatment (85.7%), most commonly through behavioral modifications, and post-stenting, increased use of medications such as GLP-1 receptor agonists and surgical interventions. Despite these efforts, weight loss was not associated with differential outcomes. Participants who lost weight (at least 10%) and those who did not experienced similar improvements across all key clinical endpoints for 21 subjects (of 39 subjects implanted with the River Stent) with long-term follow-up data.

Table 21: Self-Reported Weight Loss Strategies

Weight Loss Strategy	Pre-Stenting Within the Last 12 Months (n = 13)	Post-Stenting Within the Last 12 Months (n = 21)
Behavioral or lifestyle modification	84.6% (11/13)	81.0% (17/21)
Medications	23.1% (3/13)	38.1% (8/21)
GLP-1 receptor agonists	0% (0/13)	62.5% (5/8)
Weight loss surgery	0% (0/13)	19.0% (4/21)
Bariatric surgery	0% (0/13)	75.0% (3/4)
Other	7.7% (1/13)	14.3% (3/21)
Total	**84.6% (11/13)**	**85.7% (18/21)**

No analyses were performed for sex-, age-, race-, ethnicity-, or any other relevant characteristic-specific subgroups.

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 34 investigators of which none were full-time or part-time employees of the sponsor and 2 investigators 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: 0
- Significant payment of other sorts: 0
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 2

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted and analyzed 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. SAFETY AND PROBABLE BENEFIT ANALYSIS

A. Probable Benefit Conclusions

In "The River Trial," patients received benefit from the device with respect to the primary probable benefit endpoint. The composite primary probable benefit endpoint was met for 54.5% (12/22) of subjects with observed reliable visual field data and data available for all elements of the composite primary probable benefit endpoint. At a component level, 88.9% (24/27) of subjects showed an absence of significant (> 50%) stenosis of the stented sinus and of new significant stenosis of other cerebral venous sinuses on RCV. Additionally, 88.9% (24/27) of subjects had a decrease of trans-stent pressure gradient (difference between the pressure measured in the torcula, proximal to the stent, and the pressure measure in the sigmoid sinus, proximal to the

stent) to less than 8 mmHg, and 73.1% (19/26) of subjects experienced clinically relevant improvement in headaches or vision.

Additionally, 21 of the 39 subjects enrolled in "The River Trial" had longer-term follow-up data available for 3- to 5-years post implantation. Of these 21 subjects, 85.71% (18/21) of the subjects met the primary probable benefit endpoint.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in a clinical study conducted to support HDE approval as described above.

The primary safety endpoint, MAE rate at 1 year, had an observed rate of 5.4% (2/37) [95% confidence interval: (0.7%, 18.2%)]. The upper 95% confidence limit was lower than the pre-specified performance goal of 51.7%; therefore, the primary safety endpoint was met ($p < 0.0001$, one-sided exact binomial test).

As discussed in **Table 12** above, rates of serious adverse events were relatively low. New venous sinus stenosis was reported in 11.5% (3/26) of subjects at 1 year, including one new stenosis of the transverse sinus and two superior sagittal sinus stenosis; all 3 stenoses were adjacent to the torcula. One additional subject had a CSF shunt placed after 6 months for a new venous sinus stenosis in the superior sagittal sinus for a total new venous sinus stenosis rate of 14.3% (4/28). There were no in-stent stenoses observed in the cohort with 1-year RCVM data.

C. Probable Benefit-Risk Conclusions

The probable benefits of the River Stent System are also based on data collected in a clinical study conducted to support HDE approval as described above. The probable benefits include reduction in symptoms related to headache and vision loss. Additional outcome measures supporting probable benefit include absence of significant stenosis (> 50%) and decrease in trans-stent pressure gradient.

The probable risks of the River Stent System are also based on data collected in a clinical study conducted to support HDE approval as described above. The risks of the device include procedural risks associated with placing the stent (e.g., infection, vascular damage, stenosis) and worsening IIH. The probable risks of the device are presented in section VIII of this SSPB document and the serious adverse events and the device and procedure related adverse events observed in the clinical study of the River Stent System are presented in Tables 12 and 13.

Additional factors to be considered in determining probable risks and benefits for the River Stent System included the high quantity of missing data elements for the

primary probable benefit endpoint which increases the uncertainty around the extent of benefit received by the device. In the clinical study, 19 of 39 subjects had missing data for the 1-year follow-up time point and 18 of 39 subjects for the 3- to 5-year follow-up time points. Only 22 of 39 subjects enrolled and treated in the study had CSF opening pressure measurements at the 1-year visit and 4 of 22 (18%) subjects reported CSF opening pressures > 25 cm H_2O at the 1-year visit. Additionally, "The River Trial" implemented a single-arm study design, which does not allow for direct comparison to alternative surgical therapies (e.g., CSF shunting, ONSF) for IIH patients who have failed medical therapy. It should be noted that "The River Trial" enrolled patients from 2018 to 2021 and significant advancements in weight loss medications for treatment of obesity have occurred since that time. In particular, obesity is a known contributor to worsening symptoms in IIH patients, and reduction in obesity may lessen IIH symptoms and may impact the expected benefits received from the device.

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, given the available information above, the data support that for the indications for use of the device the probable benefits of the device outweigh the probable risks. The River Stent System is indicated for stenting of the venous sinus in adult patients (22 years of age or older) with idiopathic intracranial hypertension (IIH) who have failed medical therapy, have a significant stenosis of the venous sinus (> 50% stenosis and pressure gradient ≥ 8 mmHg), and have an upstream venous sinus diameter between 5 mm and 8.5 mm. Patients must also meet one or both of the following criteria:

- Intractable headache (severe impact with score > 59 on the Headache Impact Test (HIT)-6 scale) and papilledema or a history of papilledema and medical therapy failure for IIH for at least 6 months. Patients who are obese (BMI ≥ 30) must also have completed a weight management program including behavioral therapy, nutritional counseling, and/or medication support for at least 6 months, without achieving adequate relief of their IIH symptoms.
- Moderate to severe papilledema (Frisén grade ≥ 2), transient visual obscuration, or 6^{th} nerve palsy who have failed medical therapy and in the opinion of the treating ophthalmologist are losing vision or at risk of losing vision.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and probable benefit of the River Stent System for the indications for use identified above.

Therefore, it is reasonable to conclude that 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 Neurological Devices Panel of the Medical Devices Advisory Committee because this HDE does not raise unanticipated safety issues. Therefore, it was determined that this application does not need to be submitted to the advisory committee.

XIV. CDRH DECISION

CDRH has determined that, based on the data submitted in the HDE, the River Stent 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 March 30, 2026. The final clinical conditions of approval cited in the approval order are described below.

Post-Approval Study - Continued Follow-up of "The RIVER Trial": The study will consist of all living patients who were enrolled under "The RIVER Trial" investigational device exemption (IDE) G180008 who re-consent for long-term follow-up. The objective of this study is to characterize clinical outcomes of all patients implanted with the River Stent through 5 years. Long-term follow-up data collected according to the IDE protocol will be used to provide safety and probable benefit information on the durability and safety of treatment using the River Stent System. As stipulated in the IDE protocol, follow-up assessments will include adverse event assessment, contrast enhanced magnetic resonance venography of the stented vessel for absence of significant stenosis or new stenosis, and clinically relevant improvement in the main clinical outcome per specific inclusion criteria for headache or ophthalmic enrollment criteria in "The River Trial."

The applicant's manufacturing facility was inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820), which was in effect at the time of the inspection. As of February 2, 2026, the revised part 820, referred to as the Quality Management System Regulation (QMSR), is effective.

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.