Clinical Investigation Plan Cover Page

NCT Number: NCT05330468
RC-PMCF
Regent China Post-Market Clinical Follow-up Study
Study Document Name: RC-PMCF Clinical Investigation Plan
Date: 24-May-2022

Sponsor

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Clinical Investigation Plan

[redacted]

Regent China Post-Market Clinical Follow-up Study

[redacted]	[redacted]
Planned Number of Sites and Region(s)	Up to 10 sites in China
Clinical Investigation Type	Prospective, observational, multi-center post-market clinical follow-up study
[redacted]	[redacted]
[redacted]	[redacted]
	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Clinical Investigation Plan

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I have read and agree to adhere to the clinical investigation plan and all regulatory requirements applicable in conducting this clinical investigation.

Site Principal Investigator

Printed name:
Signature:
Date:

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COMPLIANCE STATEMENT:

This study will be conducted in accordance with this Clinical Investigational Plan, the Declaration of Helsinki and the National Medical Products Administration (NMPA) applicable regulations. The most stringent requirements, guidelines or regulations must always be followed. The conduct of the study will be approved by the appropriate Ethics Committee (EC) of the respective clinical site and as specified by local regulations.

Clinical Investigation Plan

1.0 INTRODUCTION

This document is the Clinical Investigation Plan (CIP) for the Regent China Post-Market Clinical Follow-up (RC-PMCF) Study. RC-PMCF is a prospective, multi-center observational study of the safety and performance of the Regent™ Mechanical Heart Valve (Regent MHV) used as a replacement valve in patients with a diseased, damaged, or malfunctioning aortic valve. This clinical study is sponsored by Abbott.

The purpose of the RC-PMCF study is to meet the post-market clinical follow-up (PMCF) requirements of the National Medical Products Administration (NMPA). The primary objective of this clinical study is to confirm the safety and performance of Abbott's Regent MHV for the replacement of native or prosthetic aortic valves in a Chinese population. The RC-PMCF study will prospectively follow 200 subjects implanted with a Regent MHV during surgical replacement of the aortic valve at up to 10 clinical centers through 5 years post-implant.

This clinical investigation will be conducted in accordance with this CIP. All investigators involved in the conduct of the clinical investigation will be qualified by education, training, or experience to perform their tasks, and this training will be documented appropriately.

1.1 Background and Rationale

1.1.1 Background

Surgical intervention is one of the most effective therapies currently available for valvular heart disease (VHD) and has a significant survival benefit with relatively low perioperative mortality and morbidity. It is estimated that there are over 300,000 heart valve replacement surgeries performed worldwide each year[1], and this number is expected to triple by 2050.[2] Mechanical heart valve replacement is one of the options for surgical intervention and has been used for over 40 years to successfully treat VHD. Abbott's MHVs have been implanted in nearly 3 million patients and are estimated to account for 34% of implants in patients under the age of 30 undergoing aortic valve surgery.[2]

Historically, the clinical experience of more than 40 years with the Abbott MHVs has been favorable.[3-7] Clinical outcomes have demonstrated that the bileaflet design is more durable than bioprosthetic valves[1,8] and can last over 30 years.[1]

The Regent MHV is indicated for patients requiring the replacement of a diseased, damaged, or malfunctioning native aortic heart valve. It may also be used as replacement for previously implanted aortic prosthetic heart valves. Patients with failing aortic valves require intervention to avoid heart failure and related adverse events (AEs) such as mortality. Recommendations from clinical practice guidelines and consensus statements published by global heart and cardiology societies suggest surgical interventions, including valve replacement, in symptomatic patients with aortic stenosis[9-11] or aortic regurgitation.[9,10] Without intervention, patients with a malfunctioning aortic valve have a poor long-term prognosis.

The safety and performance of the Regent MHV have been previously established,[3,5,12-24] and the clinical evidence demonstrates continued safety and performance of the Regent MHV when used under the conditions and for the purposes intended. However, the Regent MHV has not been evaluated in a

prospective study in the Chinese population. The purpose of the RC-PMCF study will confirm the safety and performance of the Regent MHV in a Chinese patient population.

1.1.2 Rationale for Conducting this Clinical Investigation

The objective of this study is to confirm the continued safety and performance of the Regent MHV to meet the PMCF requirements of the NMPA.

Device safety will be evaluated by comparing freedom from valve-related mortality in subjects implanted with a Regent MHV during aortic valve replacement to predefined clinical acceptance criteria based on the surgical literature. Regent MHV device performance will be evaluated based on durability by comparison of valve-related reintervention in the replaced valve to predefined clinical acceptance criteria based on the surgical literature.

2.0 CLINICAL INVESTIGATION OVERVIEW

2.1 Clinical Investigation Objective

The objective of this clinical investigation is:

- To confirm the long-term safety and performance of Abbott Medical's Regent, model AGN-751 and AGFN-756, for replacement of native or prosthetic aortic valves in a Chinese population.

2.2 Device Used in the Clinical Investigation

2.2.1 Name of the Device Used

Regent MHV models to be used in this study are listed in Table 1. Each device is available in multiple sizes to allow treatment of native or prosthetic valve annuli with varying dimensions.

Table 1. List of Devices Used

Device name	Model Number/Sizes	Manufacturer	Market released
Regent™– Standard cuff	AGN-751 Sizes 17-29mm	Abbott (formerly SJM) 177 County Road B East, St. Paul, MN 55117	United States (2002) European Union (1999) China (2007) Canada (2000) Australia (2001) Japan (2004) Brazil (2008)
Regent™ – FlexCuff™	AGFN-756 Sizes 17-29mm		

2.2.2 Indication for Use

The Regent MHV is indicated for use as a replacement valve in patients with a diseased, damaged, or malfunctioning aortic valve. This device may also be used to replace a previously implanted aortic prosthetic heart valve.

2.2.3 Description of the Device(s) Under Investigation

The Regent MHV is a low-profile, center-opening device composed of a pyrolytic carbon orifice and two pyrolytic carbon elliptically shaped carbon leaflets. A sewing cuff fabricated of knitted polyester fabric is attached to the orifice. Figure 1 represents the general construction of the leaflet and orifice pivot design of the Regent MHV.

Figure 1. General Construction of the Regent MHV

[redacted]

Figure 2. Leaflet Positioning Within Orifice

The cuff material allows for rapid, controlled endothelial ingrowth over the sewing cuff surface. The sewing cuff is attached to the carbon orifice by a radiopaque metal band and is available in Standard Cuff and FlexCuff™ configurations. The FlexCuff™ provides an extended flange area for suture placement. Three suture markers are located on the valve sewing cuff to provide reference points for valve orientation and suture placement.

Additional information regarding the Regent MHV is available in the Instructions for Use (IFU).

3.0 CLINICAL INVESTIGATION DESIGN

The RC-PMCF is designed to meet the PMCF requirements of the NMPA. This is a prospective, observational, multi-center study of subjects clinically indicated for implantation of a Regent MHV. Two hundred subjects that enroll and undergo surgical aortic valve replacement using a commercially available Regent MHV will participate.

Study enrollment will occur at up to 10 centers in China. The study will enroll subjects expected to be implanted with a Regent MHV who meet all study eligibility requirements. Subjects who do not undergo the Regent MHV implant within 60 days of enrollment will be withdrawn from the study and will not contribute to the study sample size.

Subjects will be followed for 5 years post-implant; [redacted]. Study visits or data collection will occur at baseline, implant, discharge, 3 months, 6 months, and annually through 5 years post-implant.

3.1 Clinical Investigation Procedures and Follow-up Schedule

The process of subject screening and enrollment and the timing of data collection by study visits are summarized in **Figure 3**. Scheduled data collection will occur at a pre-implant baseline visit, implant, discharge, 3 months, 6 months, and then annually through 5 years post-implant.

[redacted]

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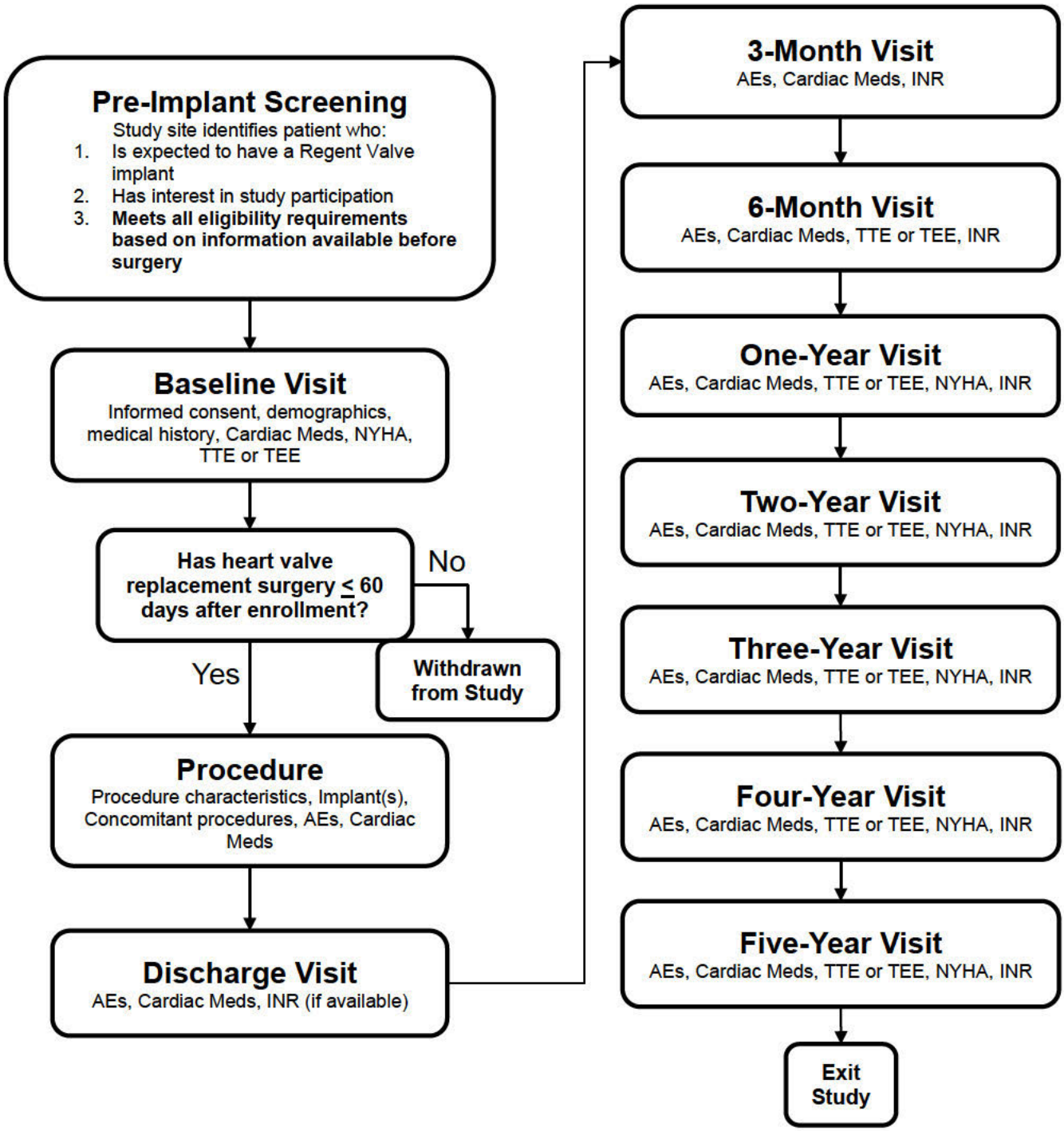
Figure 3: Clinical Investigation Flow Chart



3.2 Measures Taken to Avoid and Minimize Bias

The study will include the following measures to minimize bias in the conduct of the study and analysis of clinical data:

- Inclusion and exclusion criteria are broad to reflect the population being treated and comparable to the literature
- Consideration of subjects assessed for aortic valve replacement at each site for inclusion in the study
- Expected values for the primary safety and performance endpoints have been predefined from a systematic literature review (Section **Error! Reference source not found.**).
- Maintaining high rates of follow-up compliance

3.3 Suspension or Early Termination of the Clinical Investigation

While no formal statistical rule for early termination of the clinical investigation for insufficient effectiveness of the device under investigation is defined, the Sponsor reserves the right to discontinue the clinical investigation at any stage or reduce the follow-up period with suitable written notice to the Investigator. A possible reason may include, but is not limited to, the cancellation of further product development.

3.3.1 Subject Follow-up for Suspension or Early Termination of the Study

If the Sponsor suspends or prematurely terminates the clinical investigation at an individual site in the interest of safety, the Sponsor will inform all other Principal Investigators.

If suspension or premature termination occurs, the Principal Investigator or authorized designee will promptly inform the enrolled subjects at his/her siteand return patients to their appropriate standard medical treatment with device-related AEs reported to the Sponsor per local vigilance reporting requirements.

A Principal Investigator, IRB/EC, or regulatory authority may also suspend or prematurely terminate participation in the clinical investigation at the investigational site(s) for which they are responsible. The investigators will follow the requirements specified in the Clinical Trial Agreement.

If a suspended investigation is to be resumed, a prior approval should be obtained from the IRB/EC and a notification should be sent to the regulatory bodies as applicable. If subjects were informed of suspension, they shall be informed of the resumption of the clinical investigation.

4.0 ENDPOINTS

The two primary endpoints and the descriptive endpoints in this clinical investigation have been chosen based on safety and performance measures reported in the mechanical heart valve literature.[redacted]

4.1 Primary Endpoints and Rationale

The primary safety endpoint is freedom from valve-related mortality at 5 years. Reasons for selection of this primary safety endpoint include its correlation with severe device- and procedure-related adverse events and the frequent reporting of this outcome in the published literature on surgical MHVs.[redacted]

The primary performance endpoint is freedom from valve-related reoperation at 5 years. Reasons for selection of reoperation on the MHV is an indicator of both the performance and durability of the original MHV implant procedure and is often reported in the published literature on MHVs.[redacted]

4.2 Descriptive Endpoints

This section lists descriptive endpoints that will be summarized using descriptive statistics and compared to the objective performance criteria as defined in ISO5840-2:2021 for mechanical heart valves or acceptance criteria if appropriate.

- Annualized rate from the following events from implant through five years post-implant:
  - All-cause mortality
  - Reintervention
  - Major bleeding
  - Thromboembolism
  - Valve thrombosis
  - Endocarditis (Operated Valve)
  - Major Paravalvular Leak

- NYHA (New York Heart Association) Functional Class at baseline and annually post-implant

5.0 SUBJECT SELECTION AND WITHDRAWAL

5.1 Subject Population

This clinical investigation will enroll male and female subjects who will be undergoing replacement of a native or prosthetic aortic heart valve. Patients must meet all general eligibility criteria and provide written informed consent prior to sites conducting any investigation-specific procedures not considered standard of care.

5.2 Subject Screening and Informed Consent

5.2.1 Subject Pre-Implant Screening

A patient who satisfies all eligibility criteria prior to informed consent will be invited to be enrolled in the clinical investigation.

5.2.2 Informed Consent

The Investigator or his/her authorized designee (if applicable) will conduct the Informed Consent process, as required by applicable regulations and the center's IRB/EC. This process will include a verbal discussion with the patient on all aspects of the clinical investigation that are relevant to the

[redacted]

patient's decision to participate, such as details of clinical investigation procedures, anticipated benefits, and potential risks of clinical investigation participation. Sites must inform patients about their right to withdraw from the clinical investigation at any time and for any reason without sanction, penalty, or loss of benefits to which the patient is otherwise entitled. Withdrawal from the clinical investigation will not jeopardize their future medical care or relationship with the Investigator.

During the discussion, the Principal Investigator or his/her authorized designee will avoid any improper influence on the patient and will respect the patient's legal rights. Financial incentives will not be given to patients. Patients may be compensated for time and travel directly related to their participation in the clinical investigation. The site shall provide the patient with the Informed Consent Form (ICF) written in a language that is understandable to the patient and that has been approved by the center's IRB/EC. The patient shall have adequate time to review, ask questions, and consider participation. The Principal Investigator or his/her authorized designee will make efforts to ensure that the patient understands the information provided. If the patient agrees to participate, they must sign and date the ICF, along with the person obtaining the consent prior to any clinical investigation-specific procedures. The site will file the signed original copy of Informed Consent Form in the patient's hospital or research charts and provide a copy to the patient.

If study-specific procedures are conducted and/or data were collected from the subject without informed consent, sites should report any failure to obtain informed consent from a patient to the Sponsor within 5 working days and to the reviewing center's IRB/EC according to the IRB's/ EC's reporting requirements.

If, during the clinical investigation, new information becomes available that can significantly affect a subject's future health and medical care, the Principal Investigator or his/her authorized designee (if applicable) will provide this information to the subject. If relevant, sites will ask the subject to confirm their continuing by providing informed consent revision(s) in writing.

5.2.2.1 Special Circumstances for Informed Consent

This clinical investigation excludes individuals unable to make the decision to participate in a clinical investigation on their own or who are unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of retaliatory response. This clinical investigation excludes individuals under the age of 18 from the clinical investigation population.

The clinical investigation excludes individuals unable to read or write. The clinical investigation excludes pregnant or breastfeeding women. All other aspects of the Informed Consent process will follow Section **Error! Reference source not found.**.

The Investigator or designee, who has been trained on the CIP, will explain the nature and scope of the clinical investigation, potential risks and benefits of participation, and answer questions for the subjects. All subjects (or legally acceptable subjects' representatives, if applicable) must sign and date the IRB/EC-approved Informed Consent form prior to any clinical investigation-specific procedures. Sites may not enroll a patient who is considered part of a vulnerable population in the investigation, except for a member of the armed forces. However, special protection must be given to these patients. When obtaining informed consent from these patients, the physician should be particularly cautious if the patient is in a dependent relationship with the physician or may consent under duress. In that case, an independent witness should be present throughout the Informed Consent process.

5.3 Eligibility Criteria

Assessment for eligibility criteria is based on medical records of the site and an interview with a candidate patient. Patients must meet ALL inclusion criteria to participate in the clinical investigation. If ANY exclusion criteria are met, the patient is excluded from the clinical investigation and cannot be enrolled.

If any clinical and/or laboratory tests are required for patient screening and are not included in a site's standard tests, they must be completed after written informed consent is obtained.

5.3.1 Inclusion Criteria

1. Patient is eligible to be implanted with Regent to replace a native or prosthetic aortic valve per Regent's IFU
2. Subject will be ≥18 years of age at time of being consented
3. Subject provides written informed consent prior to any clinical investigation-specific procedure.

5.3.2 Exclusion Criteria

1. Subject is unable to tolerate anticoagulation therapy
2. Subject has active endocarditis
3. Subject is currently participating in another clinical investigation which may interfere with the effectiveness of anticoagulation therapy
4. Pregnant or nursing subjects and those who plan pregnancy during the clinical investigation follow-up period. Women of child-bearing potential must have a documented negative pregnancy test within one week prior to enrollment
5. Subject has anomalous anatomy or medical, surgical, psychological or social history or conditions that, in the Investigator's opinion, could limit the subject's ability to participate in the clinical investigation or to comply with follow-up requirements of the clinical investigation results
6. Subject is unable to read or write or has a mental illness or disability that impairs their ability to provide written informed consent
7. Subject's life expectancy is less than 1 year in the opinion of the Investigator

5.4 Subject Enrollment

A patient is considered enrolled in the clinical investigation from the moment the patient provides written informed consent.

5.5 Subject Withdrawal and Discontinuation

Each subject enrolled shall remain in the clinical investigation until completion of the required follow-up period; however, a subject's participation in any clinical investigation is voluntary, and the subject has the right to withdraw at any time without penalty or loss of benefit. Conceivable reasons for discontinuation may include, but not be limited to, the following:

- Subject death
- Subject did not undergo the Regent MHV implant surgery within 60 days of enrollment
- Subject had an unsuccessful implant of the Regent MHV
- Subject voluntary withdrawal
- Subject lost-to follow-up as described below
- Subject's follow-up is terminated according to Section 3.3

Note: Subjects who undergo a surgical reintervention following the implant of the Regent MHV will not be withdrawn from the study as a consequence of the reintervention. Such subjects will continue follow-up until completing their last scheduled study visit unless withdrawn from the study for another reason.

Sites must notify the Sponsor of the reason(s) for subject discontinuation. Investigators must also report this to their respective IRB/EC as defined by their institution's procedure(s).

No additional follow-up is required or data recorded from subjects once withdrawn from the clinical investigation, except for the status (deceased/alive).

However, if a subject withdraws from the investigation due to problems related to the safety or performance of the device under observation, the Investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical investigation.

Lost-to-Follow-up

If the subject misses two consecutive scheduled follow-up time points and the attempts at contacting the subject detailed below are unsuccessful, then the subject is considered lost-to-follow-up. Site personnel shall make all reasonable efforts to locate and communicate with the subject (and document these efforts in the source documents), including the following, at each contact time point:

- A minimum of two telephone calls on different days over the specified follow-up windows to contact the subject should be recorded in the source documentation, including date, time and initials of site personnel trying to make contact.
- If these attempts are unsuccessful, the site should send a letter (certified if applicable) to the subject.
- If a subject misses one or more non-consecutive follow-up contact time points, it will be considered a missed visit. The subject may then return for subsequent visits. If the subject misses two consecutive time points and the above-mentioned attempts at communicating with the subject are unsuccessful, the subject will be considered lost-to-follow-up.

Note: Telephone contact with General Practitioner, non-clinical investigation cardiologist, or relative will be considered as subject contact for the purpose of collecting vital status information. The center shall retain records of the contact.

5.6 Number of Subjects

The clinical investigation will enroll 200 eligible implanted subjects. No site may enroll more than 40% of the total subjects. Allowing for subjects who provide written informed consent but are withdrawn without undergoing a Regent MHV implant, RC-PMCF study enrollment is expected to be less than 250 subjects.

5.7 Total Expected Duration of the Clinical Investigation

[redacted]

6.0 TREATMENT AND EVALUATION OF ENDPOINTS

6.1 Baseline

The following baseline data will be collected after informed consent is obtained.

- Informed consent process (Section **Error! Reference source not found.**)
- Indication for aortic valve replacement
- Demographics
- Medical history
- Cardiac medications
- Physical examination
- NYHA Classification
- Transesophageal echocardiography (TEE) or transthoracic echocardiography (TTE), per site standard of care

The PI, or delegated study personnel, is responsible for screening potential subjects to determine eligibility for the study. Enrollment information (consent information, inclusion/exclusion information) will be recorded in the subject's medical record and on the Enrollment Case Report Form (CRF). Every effort shall be made to submit the Enrollment CRF within one week of enrollment.

If a subject is consented and undergoes study-specific testing (i.e., testing that otherwise would not be conducted) but does not qualify for the study, the subject will be considered a screen failure and withdrawn from the study.

6.2 Index Procedure

Subjects that meet inclusion and exclusion criteria and provide written informed consent but do not undergo a Regent MHV implant within 60 days of enrollment will be withdrawn without further follow-up required. The following information will be collected during the index procedure.

- Procedure characteristics (e.g., surgeon, access approach, CPB time)
- Regent MHV implant
- Concomitant procedures
- Adverse Events
- Cardiac medications

6.3 Discharge/Post Procedure

The discharge visit will take place prior to hospital discharge or within 7 days after the procedure, whichever occurs first. If the subject is expected to be discharged over the weekend, the visit may be completed on the last weekday prior to discharge.

- Cardiac medications
- International Normalized Ratio (INR) Level (if available)
- Adverse events

6.4 Follow-up Assessments

Required clinical investigation follow-up visits will be performed at the following intervals. The visit window intervals are determined by the date of procedure.

- 3-month visit (90 days ± 30 days)
- 6-month visit (180 days ± 30 days)
- 1-year visit (365 days ± 60 days)
- 2-year visit (731 days ± 60 days)
- 3-year visit (1096 days ± 60 days)
- 4-year visit (1461 ± 60 days)
- 5-year visit (1826 + 60 days)

Follow-up visits can be performed at any point in the window. The subject should be followed at the investigational site where the subject was enrolled and may be followed at another investigational site only with prior agreement from both that site's PI and the Sponsor. All visits and assessments should be completed even if the subject is hospitalized.

During each visit, the following data will be collected:

- Cardiac medications
- TEE or TTE, per site standard of care (6 months and annual visits)
- INR Level

- NYHA Classification (annual visits)
- Adverse events

6.4.1 Follow-up CIP Medications

Antiplatelet/anticoagulation and other medications should be administered per the local institutional standard of care at the investigational site.

6.4.1.1 INR Level Monitoring

INR levels should be maintained per the local institutional standard of care (SOC). INR levels should be recorded per SOC monthly for 3 months after implant. Three months after implant, INR levels should be recorded every 3 months. The site will telephone the subject to obtain INR levels that have been completed as per SOC and record on the INR Log CRF.

6.4.2 Schedule of Events

Table 2 provides a tabulated schedule of the study-required activities and standard of care data collection in the clinical study.

Table 2: Table of Assessments

CIP Activity	Baseline	Procedure (day 0)	Discharge (0-7 days)	3 months (90 ± 30 days)	6 months (180 ± 60 days)	1 year (365 ± 60 days)	2 year (731 ± 60 days)	3 year (1096 ± 60 days)	4 year (1461 ± 60 days)	5 year (1826 + 60 days)
Informed Consent Process	X									
Demographics	X									
Physical Examination	X									
Medical History	X									
Replacement indication	X									
Pregnancy Test	X									
Regent MHV device implant		X								
Concomitant intervention		X								
Procedure Characteristics		X								
TTE or TEE[1]	X				X	X	X	X	X	X

NYHA Functional Classification	X					X	X	X	X	X
Cardiac Medication	X	X	X	X	X	X	X	X	X	X
INR Level[2]			(X)	X	X	X	X	X	X	X
Adverse Event		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Deviation		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Device Deficiency		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Withdrawal		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Death		(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)

(X) – as applicable
[1]TTE or TEE should be completed and collected for all cardiac SAEs and device-related AEs
[2]Site to telephone subject monthly for 3 months post-implant and then every 3 months to collect INR level completed as SOC

7.0 Adverse Events

To comply with worldwide standards and guidelines on clinical investigation adverse event reporting, the Sponsor has adopted uniform and worldwide applicable standard definitions and reporting timelines to be used and adhered to by the investigators.

7.1 Definition

7.1.1 Adverse Event

An Adverse Event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational medical device.

As part of ISO14155 Section 3.2, the Adverse Event definition has the following notes:

Note 1: This definition includes events related to the investigational medical device or the comparator.

Note 2: This definition includes events related to the procedures involved.

Note 3: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

7.1.2 Serious Adverse Event

Serious Adverse Event is an AE that led to any of the following:

a) Death,

b) Serious deterioration in the health of the subject that resulted in any of the following:

1. life-threatening illness or injury

2. permanent impairment of a body structure or a body function
3. hospitalization or prolongation of patient hospitalization
4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
5. chronic disease

c) Fetal distress, fetal death, or a congenital physical or mental impairment or birth defect.

Note: A planned hospitalization for a pre-existing condition, or a procedure required by the CIP without a serious deterioration in health, is not considered an SAE.

7.1.3 Device Deficiency/Device Malfunction

Device deficiency is defined as any inadequacy in the identity, quality, durability, reliability, usability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in the information supplied by the manufacturer, including labeling.

Note 1: The definition includes device deficiencies related to the investigational medical device or the comparator.

A device malfunction is the failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP.

7.2 Device Relationship

Whether there is a reasonable possibility that the product or device under investigation caused or contributed to an AE is to be **determined by the Investigator** and recorded on the appropriate CRF form. Determination should be based on the assessment of temporal relationships, evidence of alternative etiology, medical/biologic plausibility and patient condition (pre-existing condition).

7.3 Adverse Event and Device Deficiency/Device Malfunction Reporting

7.3.1 Adverse Event Reporting

Safety surveillance and reporting starts as soon as the subject is enrolled in the clinical investigation. Adverse events will not be collected for screen failure subjects. Safety surveillance and reporting will continue until sites perform the last follow-up visit, the subject is deceased, the subject concludes participation in the clinical investigation, or the subject withdraws from the clinical investigation. Sites should update additional information regarding an adverse event on the appropriate CRF.

Unchanged, chronic, non-worsening or pre-existing conditions are not AEs and should not be reported.

For the purpose of this trial, the following adverse event types will be reported:

- Adverse events considered related to the implanted Regent MHV
- All serious adverse events

In addition, the following endpoint-related adverse events meeting the Akins[25] criteria defined in Appendix II will be reported regardless of seriousness or relatedness:

- Death – all-cause and valve-related mortality
- Reinterventions of the replaced valve
- Major bleeding
- Thromboembolism
- Valve thrombosis
- Endocarditis (operated valve)
- Major paravalvular leak

The Investigator will assess the events for relationship to the device and relationship to the procedure.

The Sponsor will provide an offline form to allow the Investigator to report SAEs in the event the entry cannot be made in the EDC. This does not replace the EDC reporting system. Sites must still enter all information in the EDC system as soon as feasible.

SAE Reporting

The Investigator must report all SAEs to the Sponsor as soon as possible but no later than outlined below.

Clinical Site	Reporting timelines
All Sites	Investigators must report SAEs to the Sponsor no later than 24 hours from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.

Sites must record the date the site staff became aware that the event met the criteria of an SAE in the source document. The Investigator will report the SAE to the local IRB/EC according to the institution's IRB/EC reporting requirements.

7.3.2 Device Deficiency/Malfunction Reporting

Sites should report all device deficiencies/malfunctions on the appropriate CRF form.

The Investigator must report all device deficiencies/malfunctions to the Sponsor as soon as possible but no later than outlined below.

Clinical Sites	Reporting timelines
All Sites	Sites must report device deficiencies/malfunctions to the Sponsor no later than 3 calendar days from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.

Sites must report device deficiencies/malfunctions to the IRB/EC per the investigative site's local requirements.

Sites should return the device, if not implanted or not remaining in the subject, to the Sponsor.

Sites will have access to an offline form to allow the Investigator to report device deficiencies/malfunctions if sites cannot enter the information in the EDC system. This does not replace the EDC reporting system. Sites must still enter all information in the EDC system as soon as feasible.

7.3.3 Adverse Event Reporting to Regulatory Authorities by the Sponsor

The Sponsor shall evaluate and report safety information to investigational sites, IRBs/ECs, and regulatory authorities as follows:

1. Within 7 days of learning that a life-threatening SAE or death related to the study device occurred
2. Within 15 days of learning that a non-life-threatening, device-related SAE occurred, if the device may have other serious safety risks

In case of any new information that may affect subject safety, the implementation of the clinical investigation, or the IRBs/ECs' opinion, the Sponsor shall promptly amend the CIP, the ICF, and other relevant documents and submit them to the Ethics Committee for review.

In case of any device-related SAEs on a large scale or any other major safety problems, the Sponsor shall suspend or terminate the clinical investigation and notify the investigational sites, IRBs/ECs, and regulatory authorities.

8.0 STATISTICAL CONSIDERATIONS

The following section describes the statistical methods for the clinical investigation. Additional details on statistical analysis are maintained in a separate statistical analysis plan.

8.1 Analysis Populations

[redacted]

8.2 Statistical Analyses

8.2.1 Primary Safety Endpoint Analysis

The primary safety endpoint is freedom from valve-related mortality. [redacted]

Reasons for selection of this primary safety endpoint include its objective nature, its correlation with severe device- and procedure-related adverse events, and the frequent reporting of this outcome in the

[redacted]

published literature on surgical valve replacement. [redacted]

8.2.2 Primary Performance Endpoint Analysis

The primary performance endpoint is freedom from valve-related reoperation. [redacted]

Freedom from reintervention on the replaced valve is an indicator of both the performance and durability of the original replacement procedure and is often reported in the surgical literature on valve replacement. [redacted]

8.2.3 Descriptive Endpoints

The following descriptive endpoints will be summarized as % events per valve-year. Major bleeding, thromboembolism, valve thrombosis, endocarditis and major paravalvular leak will be assessed at 5 years, and descriptively compared to 2 times the objective performance criteria as defined in ISO5840-2:2021 for mechanical heart valves. All-cause mortality and reintervention will be assessed at 5 years, and descriptively compared to acceptance criterion, as outlined below:

- Annualized rate of all-cause mortality (Acceptance criterion = [redacted])
- Annualized rate of reintervention (Acceptance criterion = [redacted])
- Annualized rate of major bleeding (OPC = 1.6% per valve-year)
- Annualized rate of thromboembolism (OPC = 1.6% per valve-year)
- Annualized rate of valve thrombosis (OPC = 0.1% per valve-year)
- Annualized rate of endocarditis (OPC = 0.3% per valve-year)
- Annualized rate of major paravalvular leak (PVL) (OPC = 0.3% per valve-year)

Valve dysfunction will be assessed by echocardiogram at 6 months and annual visits.

NYHA Classification will be assessed at baseline and annual visits.

8.3 Sample Size Calculation

Two hundred implanted subjects will be enrolled. [redacted]

8.4 Timing of Analysis

Data analyses will be performed when all subjects have either completed 5-year follow-up or have withdrawn from the study. In addition, study progress and data may be summarized and reported as needed.

8.5 Subgroup Analysis

No subgroup analyses are planned for this clinical investigation.

8.6 Multiplicity

No formal hypothesis testing will be performed in this study; therefore, adjustments for multiplicity will not be made.

8.7 Procedures for Accounting for Missing Data

Every effort will be made to collect all required data. All data available for the endpoints specified among the analysis population will be used. Subjects who do not experience an event will be censored at their last known event-free time point. Descriptive endpoints will be analyzed on the available data without imputation.

8.8 Planned Interim Analysis

No interim analyses are planned for this study. An annual study report will be generated during each calendar year. All enrollment and follow-up data collected since the study inception up till a pre-determined cut-off date will be prepared in the annual study report and submitted to NMPA to support the renewal of Regent registration. A final report will be prepared following study completion.

8.9 Deviations from Statistical Plan

The Sponsor will document any major changes to the statistical plan in an amendment to the statistical plan and any less significant changes to the planned analyses in the final report.

9.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/institution will permit direct access to source data/documents for performing clinical investigation-related monitoring, audits, IRB/EC review and regulatory inspections.

Subjects providing informed consent are agreeing to allow clinical investigation monitors or regulatory authorities, including foreign countries, to review in confidence any records identifying the subjects in this clinical investigation. This information may be shared with regulatory agencies; however, the Sponsor undertakes not to otherwise release the subject's personal and private information.

10.0 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Selection of Clinical Sites and Investigators

The Sponsor will select investigators qualified by training and experience to participate in the clinical investigation. Sites will be selected based upon review of a recent site assessment, if applicable, and the qualifications of the investigators who will participate in the clinical investigation.

In addition to the above, two or more medical device clinical trial institutions would be considered to carry out the clinical investigation per regulatory requirements in China. A list of the participating sites may be provided upon request.

10.2 Site Principal Investigator Responsibilities

The role of the Site Principal Investigator is to implement and oversee the management of the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical investigation. The Principal Investigator shall support monitoring and reporting to IRB/EC and local competent authorities as necessary, throughout the conduct of the clinical investigation.

The Principal Investigator is responsible for ensuring adequate training and qualification of the investigation site team and for maintaining oversight of their activities. The Principal Investigator may delegate tasks to members of the investigation site team but retains responsibility for the clinical investigation. This also applies when activities are outsourced to an external organization by the Principal Investigator, in which case, he/she shall exercise oversight to ensure the integrity of all tasks performed and any data generated by this external organization.

10.3 Clinical Investigation Finances and Agreements

Abbott will finance the clinical investigation and will compensate investigational sites for participation in the clinical investigation per the conditions of agreement between Abbott and the investigational sites.

10.4 CIP Amendments

The Sponsor will provide approved CIP amendments, if applicable, to the Investigators prior to implementing the amendment. The Principal Investigator is responsible for obtaining IRB's/EC's approval of the CIP amendment according to the instructions provided by the Sponsor with the CIP amendment.

Sites must document in writing approval of the CIP amendment by the IRB/EC prior to implementing the CIP amendment. Sites must also provide copies of this documentation to the Sponsor.

10.5 Training

10.5.1 Site Training

All Investigators and clinical investigation personnel are required to attend Sponsor training sessions, which may be conducted at an Investigator's meeting, a site initiation visit, or other appropriate training sessions. Over-the-phone or self-training may take place as required. Training of Investigators and

clinical investigation personnel will include, but is not limited to, the CIP requirements, investigational device usage, electronic case report form completion, and clinical investigation personnel responsibilities. All Investigators and clinical investigation personnel that are trained must sign a training log (or an equivalent) upon completion of the training. Prior to signing the training log, Investigators and clinical investigation personnel must not perform any CIP-related activities that are not considered standard of care at the site.

10.6 Monitoring

The Sponsor and/or designee will monitor the clinical investigation over its duration according to the CIP-specific monitoring plan, which will include the planned extent of source data verification.

Prior to initiating any procedure, the Sponsor monitor (or delegate) will ensure that the following criteria are met:

- The Investigator understands and accepts the obligation to conduct the clinical investigation according to the CIP and applicable regulations and has signed the Clinical Trial Agreement.
- The Investigator and his/her staff should have sufficient time and facilities to conduct the clinical investigation and should have access to an adequate number of appropriate subjects to conduct the clinical investigation.
- Sites must have source documentation (including original medical records) to substantiate proper informed consent procedures, adherence to CIP procedures, adequate reporting and follow-up of adverse events, accuracy of data collected on case report forms, and device information.
- The Investigator/site will permit access to such records and will maintain a monitoring visit sign-in log at the site. The Investigator will agree to dedicate an adequate amount of time to the monitoring process. The Investigator and/or research coordinator will be available for monitoring visits. It is expected that the Investigator will provide the monitor with a suitable working environment for review of clinical investigation-related documents.

10.7 Deviations from CIP

The Investigator should not deviate from the CIP for any reason except in cases of medical emergencies when the deviation is necessary to protect the rights, safety, and well-being of the subject or to eliminate an apparent immediate hazard to the subject. In that event, the Investigator will notify the Sponsor immediately by phone or in writing.

The Sponsor will not grant any waivers for CIP deviations. Sites must report all deviations to the Sponsor using the Deviation CRF. The Sponsor will monitor the occurrence of CIP deviations for evaluation of investigator compliance to the CIP and regulatory requirements and handle according to written procedures. Investigators will determine the cause of deviations, implement corrective actions and inform their IRB/EC or equivalent committee of CIP deviations in accordance with their specific IRB/EC or equivalent committee reporting policies and procedures.

In the event of repeated non-compliance, as determined by the Sponsor, a Sponsor's monitor or company representative will attempt to secure compliance by one or more of the following (and not limited to):

- Visiting the Investigator and/or delegate
- Telephoning the Investigator and/or delegate
- Corresponding with the Investigator and/or delegate

Repeated non-compliance with the signed agreement, the CIP, or any other conditions of the clinical investigation may result in further escalation in accordance with the Sponsor's written procedures, including securing compliance or, at its sole discretion, the Sponsor may terminate the Investigator's participation in the clinical investigation.

10.8 Quality Assurance Audit

A Sponsor representative or designee may request access to all clinical investigation records, including source documentation, for inspection during a Quality Assurance audit.

If an investigator is contacted by a Regulatory Agency in relation to this clinical investigation, the Investigator will notify the Sponsor immediately. The Investigator and Research Coordinator must be available to respond to reasonable requests and audit queries made during the audit process. The Investigator must provide the Sponsor with copies of all correspondence that may affect the review of the current clinical investigation (e.g., Form FDA 483, Inspectional Observations, Warning Letters, Inspection Reports, etc.). The Sponsor may provide any needed assistance in responding to regulatory audits.

10.9 Sponsor Auditing

1. The Sponsor shall prepare an audit plan as well as the operating procedures for the related duties and conduct audits in accordance with the audit plan and the operating procedures.
2. Individuals engaged in auditing (hereinafter referred to as "auditor") shall be different than those in charge of medical device development or monitoring.
3. The auditor shall prepare an audit report documenting the matters confirmed in the audit to certify and verify that the audit has been conducted and submit them to the Sponsor.

11.0 DATA HANDLING AND RECORD KEEPING

The Sponsor and/or its affiliates will maintain documentation of the systems and procedures used in data collection for the duration of the clinical investigation.

CRF data collection will be performed through a secure web portal, and only authorized personnel will access the EDC system using a unique username and password to enter, review or correct data. Passwords and electronic signatures will be strictly confidential.

The data will be subjected to consistency and validation checks within the EDC system and supplemental review by the Sponsor.

[redacted]

At the end of the clinical investigation, completed CRF images with the date-and-time stamped electronic audit trail indicating the user, the data entered, and any reason for change (if applicable) will be provided to the investigational sites, if requested.

For the duration of the clinical investigation, the Investigator will maintain complete and accurate documentation including, but not limited to, medical records, clinical investigation progress records, laboratory reports, CRFs, signed ICFs, device accountability records (if applicable), correspondence with the IRB/EC and clinical investigation monitor/Sponsor, adverse event reports, and information regarding subject discontinuation or completion of the clinical investigation.

11.1 Protection of Personally Identifiable Information

The Sponsor respects and protects personally identifiable information collected or maintained for this clinical investigation.

The Sponsor implements technical and physical access controls to ensure that Personal Information is accessible only to and processed only on a 'need to know' basis, including periodic review of access rights, and revocation of access when an individual's employment is terminated or the individual transitions to a role that does not require access to Personal Information, and appropriate restrictions on physical access to premises, facilities, equipment, and records containing Personal Information.

The Sponsor requires the investigational sites to enter only pseudonymous Personal Information (key-coded) necessary to conduct the clinical investigation, such as the patient's medical condition, treatment, dates of treatment, etc., into the Sponsor's data management systems. The Sponsor discloses as part of the clinical investigation informed consent process that some Sponsor representatives still may see Personal Information at the participating sites for technical support of the participating physicians on the device implant or procedures, monitoring and quality control purposes. All parties will observe confidentiality of Personal Information always throughout the clinical investigation. All reports and data publications will preserve the privacy of each subject and confidentiality of his/her information.

The Sponsor data management systems and processes were designed, developed, and tested according to industry standards to appropriately safeguard Confidential Information (including any Personal Information) against unauthorized access and/or interference by third parties, intrusion, theft, destruction, loss or alteration. Clinical Investigation data are encrypted in transit and at rest.

The Sponsor maintains a Privacy Incident procedure that complies in all respects with Applicable Law and industry best practices.

11.2 Data Management Plan

A Data Management Plan (DMP) will describe procedures used for data review, data cleaning, issuing and resolving data discrepancies, and database locking. If appropriate, the Sponsor may update the DMP throughout the duration of the clinical investigation. The Sponsor will track and document control all revisions.

11.3 Source Documentation

Regulations and Good Clinical Practice (GCP) require the Investigator to maintain information in the subject's original medical records that corroborates data collected on the CRFs. To comply with these regulatory requirements/GCP, sites should include the following information in the subject record at a minimum and if applicable to the clinical investigation:

- Medical history/physical condition of the subject before involvement in the clinical investigation sufficient to verify CIP entry criteria
- Dated and signed notes on the day of entry into the clinical investigation referencing the Sponsor, CIP number, subject ID number, and a statement that informed consent was obtained
- Dated and signed notes from each subject visit (for specific results of procedures and exams)
- AEs reported and their resolution, including supporting documents, such as discharge summaries, and lab results including documentation of site awareness of SAEs and of investigator assessment of device relationship for SAEs.
- Notes regarding CIP-required and prescription medications taken during the clinical investigation (including start and stop dates)
- Subject's condition upon completion of or withdrawal from the clinical investigation
- Any other data required to substantiate data entered into the CRF

11.4 Case Report Form Completion

Site research personnel trained on the CIP and CRF completion will perform the primary data collection clearly and accurately based on source-documented hospital and/or clinic chart reviews. The Investigator will ensure accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor on the CRFs and in all required reports.

Sites will collect data on all subjects enrolled into the clinical investigation.

Only authorized site personnel will be permitted to enter the CRF data through the EDC system deployed by the Sponsor. The Sponsor will use an electronic audit trail to track any subsequent changes of the entered data.

11.5 Record Retention

The Sponsor and Investigator/Site will archive and retain all documents pertaining to the clinical investigation as per the applicable regulatory record retention requirements and clauses in clinical trial agreements. The Investigator must obtain permission from the Sponsor in writing before destroying or transferring control of any clinical investigation records.

12.0 ETHICAL CONSIDERATION

12.1 Institutional Review Board/Medical Ethics Committee Review and Approval

The Principal Investigator at each investigational site will obtain IRB/EC approval for the CIP and ICF/other written information provided to the patient prior to consenting and enrolling patients in this clinical investigation. The site must receive the approval letter prior to the start of this clinical investigation and provide a copy to the Sponsor.

Sites will submit any amendments to the CIP as well as associated ICF changes to the IRB/EC and written approval obtained prior to implementation, according to each institution's IRB/EC requirements.

No changes will be made to the CIP or ICF or other written information provided to the patient without appropriate approvals, including IRB/EC, the Sponsor, and the regulatory agencies (if applicable).

Until the clinical investigation is completed, the Investigator will advise his/her IRB/EC of the progress of this clinical investigation, per IRB/EC requirements. Written approval must be obtained from the IRB/EC periodically to continue the clinical investigation, or according to each institution's IRB/EC requirements.

Sites will not perform any investigative procedures, other than those defined in this CIP, on the enrolled subjects without the written approval of the IRB/EC and the Sponsor.

13.0 CLINICAL INVESTIGATION CONCLUSION

The clinical investigation will be concluded when:

- All sites are closed AND
- The final report has been provided to investigators or the Sponsor has provided formal documentation of clinical investigation closure and written approval from sites' IRBs/ECs.

14.0 PUBLICATION POLICY

[redacted]

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15.0 RISK ANALYSIS

15.1 Anticipated Clinical Benefits

[redacted]

15.2 Foreseeable Adverse Events and Anticipated Adverse Device Effects

Risks associated with the specified device and procedure are bleeding, hemolysis, endocarditis, infections, thrombus, or thromboembolism, valve dehiscence, unacceptable hemodynamic performance (including: elevated pressure gradients, prothesis patient mismatch or transvalvular regurgitation), paravalvular leak, hemorrhagic complications secondary to anticoagulation therapy, prosthetic failure (including: pannus ingrowth (NSVD), leaflet fracture/ escape/ split/ dislodgement, and entrapped leaflet/ stuck valve/ leaflet immobility, thrombocytopenia, heart block requiring pacemaker implant, adjacent cardiac structure interference, stroke, heart failure, myocardial infarction, or death as described in the IFU. Any of these complications may require reoperation or explantation of the device. There may be risks related to the device under investigation that are unknown at present. Likewise, the exact frequency of the risk may be unknown.

15.3 Residual Risks Associated with the Device Under Investigation, as Identified in the Risk Management Report / Risk Analysis Report

Risk analysis of the Regent MHV device has been performed in accordance with the Risk Analysis Plan [redacted] and Design Failure Mode Effect Analysis [redacted] to systemically identify potential hazards associated with the design and use of this device. Based upon bench testing and prior Abbott-sponsored clinical study data, all risks have been identified and mitigated as far as possible through application of appropriate controls and inspections and determined to be within acceptable levels.

Residual risks are likewise disclosed in the IFU in the form of clear instructions of what actions to take or to avoid, to avoid a hazardous situation of harm from occurring (contra-indications, warnings, and precautions). The anticipated AEs disclosed in the IFU provide further information to enable the user, and potentially the subject, to make an informed decision that weighs the residual risk against the benefit of using the device.

15.4 Risks Associated with Participation in this Clinical Investigation

[redacted]

[redacted]

[redacted]

15.5 Steps Taken to Control or Mitigate Risks

In-depth recommendations, special precautions, and instructions regarding device handling, device placement and system removal are included in the IFU.

It is also stated in the IFU that the device should be used by or on order of a physician. This statement is interpreted to mean that the physician users are expected to be aware of the known and foreseeable safety risks associated with the use of the devices, including the surgical and/or non-surgical treatment of these conditions.

Risks associated with the use of the device under investigation are minimized through device design, investigator selection and training, and study monitoring to ensure adherence to the protocol. Sites will report all adverse events and device deficiencies to the Sponsor, and the Sponsor will monitor internally for safety surveillance purposes.

15.6 Risk to Benefit Rationale

Regent MHVs have been used for more than 20 years with good clinical outcomes. Surgical interventions including aortic root replacement with Regent MHVs are indicated in subjects with complex aortic root pathologic disease. The clinical benefits of these Regent MHVs include reduction in symptoms of aortic valve disease, improvement in hemodynamics, and longer life expectancy with improved quality of life. Regent MHVs have shown a lower rate of device failure, as well as greater durability and less structural deterioration over time than bio-prosthetic valves. Anticoagulant therapy is routinely used in subjects implanted with a Regent MHV. The use of anticoagulants increases the risk of bleeding; however, in clinical data observed from the literature, the risk of bleeding and thromboembolism associated with the MHV devices was low for subjects in whom the use of both biological and mechanical Regent MHV is possible. The clinical evidence and post-market data support a positive risk-to-benefit ratio in subjects receiving a Regent MHV for aortic root replacement.

APPENDIX I: ABBREVIATIONS AND ACRONYMS

Abbreviation	Term
AE	Adverse Event
CIP	Clinical Investigation Plan
CRF	Case Report Form
DMP	Data Management Plan
EC	Ethics Committee
EDC	Electronic Data Capture
GCP	Good Clinical Practice
ICF	Informed Consent Form
IFU	Instructions For Use
INR	International Normalized Ratio
IRB	Institutional Review Board
KM	Kaplan-Meier
MHV	Mechanical Heart Valve
NMPA	National Medical Products Administration
NYHA	New York Heart Association
OPC	Objective Performance Criteria
PI	Principal Investigator
PMCF	Post-market Clinical Follow-up
PVL	Paravalvular Leak
TEE	Transesophageal Echocardiography
TTE	Transthoracic Echocardiography
SAE	Serious Adverse Event
SOC	Standard of Care
USA	United States of America (same as US)
VHD	Valvular Heart Disease

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APPENDIX II: DEFINITIONS

The following definitions for primary and descriptive endpoint events will be used in this investigation. These definitions are taken from the Akins *et al.*[25] guidelines for adverse event reporting after cardiac valve interventions referenced in ISO 5910:2018 "Cardiovascular implants and extracorporeal systems—Cardiac valve repair devices." Note that the Akins *et al.* definition of embolism is limited to thromboembolism, which is the term used in the text of the CIP. Similarly, the Akins *et al.* definition of a bleeding event is limited to major bleeding and this terminology is used in the CIP text.

All-cause Mortality: All-cause mortality includes all deaths from any cause after a valve intervention.

Embolism: Embolism is any embolic event that occurs in the absence of infection after the immediate perioperative period. Embolism may be manifested by a neurologic event or a noncerebral embolic event. A neurologic event includes any central, new neurologic deficit, whether temporary or permanent and whether focal or global, that occurs after the patient emerges from anesthesia. A noncerebral embolic event is an embolus documented operatively, at autopsy, or clinically that produces signs or symptoms attributable to complete or partial obstruction of a peripheral artery. Intraoperative myocardial infarctions are not counted. Postoperative myocardial infarction is also not counted unless the infarction is caused by a coronary embolus (as detected by operation, autopsy, or clinical imaging). Emboli consisting of non-thrombotic material (e.g., atherosclerosis, myxoma) are not counted.

Bleeding Event: A bleeding event is any episode of major internal or external bleeding that causes death, hospitalization, or permanent injury (e.g., vision loss) or necessitates transfusion. Major bleeding unexpectedly associated with minor trauma should be reported as a bleeding event, but bleeding associated with major trauma or a major operation should not. Bleeding events are reported for all patients regardless of whether they are taking anticoagulants or antiplatelet drugs. Although total bleeding events must be reported, bleeding events can also be reported separately for those who are taking anticoagulants or antiplatelet agents and those who are not.

Operated Valve Endocarditis: Operated valve endocarditis is any infection involving a valve on which an operation has been performed. The diagnosis of operated valvular endocarditis is based on one of the following criteria: (1) reoperation with evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histologic or bacteriologic studies; (2) autopsy findings of abscess, pus, or vegetation involving a repaired or replaced valve; or (3) in the absence of reoperation or autopsy, meeting of the Duke Criteria for endocarditis. Positive blood cultures are not required for the diagnosis of operated valve endocarditis. Culture-negative endocarditis should refer only to negative blood culture results and not just the absence of any proof of infection. Morbidities associated with active infection, such as valve thrombosis, thrombotic embolus, bleeding event, or paravalvular leak, are included under this category, but not counted in other categories of morbidity.

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Reintervention: Reintervention is any surgical or percutaneous interventional catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted prosthesis or repaired valve. In addition to surgical reoperations, enzymatic, balloon dilatation, interventional manipulation, repositioning, or retrieval, and other catheter-based interventions for valve-related complications are also considered reinterventions. Indications for reintervention must be reported. Open surgical and percutaneous catheter reinterventions should be listed separately.

Valve Thrombosis: Valve thrombosis is any thrombus not caused by infection attached to or near an operated valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment. Valve thrombus found at autopsy in a patient whose cause of death was not valve-related or found at operation for an unrelated indication should also be counted as valve thrombosis.

Valve-Related Mortality. Valve-related mortality is any death caused by structural valve deterioration, nonstructural dysfunction, valve thrombosis, embolism, bleeding event, or operated valve endocarditis; death related to reintervention on the operated valve; or sudden, unexplained death. Deaths caused by heart failure in patients with advanced myocardial disease and satisfactorily functioning cardiac valves are not counted. Specific causes of valve-related deaths should be reported.

NYHA Functional Classification[26,27]

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

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APPENDIX III: DEFINING EXPECTED OUTCOMES

III.1 BACKGROUND

A literature search and review were conducted to better define expected primary endpoint outcomes for this study.

III.2 SEARCH CRITERIA AND METHODS

Expected outcomes for the primary safety endpoint and the primary performance endpoint are based on a systematic search and review of the literature on Abbott Mechanical Heart Valve surgeries indexed in the US National Library of Medicine's PubMed database.

[redacted]

III.3 SEARCH AND REVIEW RESULTS

[redacted]

III.4 EXPECTED OUTCOMES

[redacted]

III.5 LITERATURE DATA SUMMARY TABLES

Table 3. MHV Studies [redacted]

[redacted]

[redacted]

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APPENDIX IV: LITERATURE REVIEW

1. Fiedler AG, Tolis G, Jr. Surgical Treatment of Valvular Heart Disease: Overview of Mechanical and Tissue Prostheses, Advantages, Disadvantages, and Implications for Clinical Use. *Curr Treat Options Cardiovasc Med.* Feb 5 2018;20(1):7.
2. Kheradvar A, Groves EM, Goergen CJ, et al. Emerging trends in heart valve engineering: Part II. Novel and standard technologies for aortic valve replacement. *Annals of biomedical engineering.* 2015;43(4):844-857.
3. Emery RW, Krogh CC, Arom KV, et al. The St. Jude Medical cardiac valve prosthesis: a 25-year experience with single valve replacement. *Ann Thorac Surg.* Mar 2005;79(3):776-782; discussion 782-773.
4. Ikonomidis JS, Kratz JM, Crumbley AJ, 3rd, et al. Twenty-year experience with the St Jude Medical mechanical valve prosthesis. *J Thorac Cardiovasc Surg.* Dec 2003;126(6):2022-2031.
5. Minakata K, Tanaka S, Okawa Y, et al. Twenty-year outcome of aortic valve replacement with St. Jude Medical mechanical valves in Japanese patients. *Circ J.* 2015;79(11):2380-2388.
6. Saito S, Tsukui H, Iwasa S, et al. Bileaflet mechanical valve replacement: an assessment of outcomes with 30 years of follow-up. *Interactive cardiovascular and thoracic surgery.* Oct 2016;23(4):599-607.
7. Toole JM, Stroud MR, Kratz JM, et al. Twenty-five year experience with the St. Jude medical mechanical valve prosthesis. *Ann Thorac Surg.* May 2010;89(5):1402-1409.
8. Cigarroa R, Elmariah S. Anticoagulation Management After Transcatheter and Surgical Valve Replacement. *Curr Treat Options Cardiovasc Med.* Apr 11 2018;20(5):42.
9. Falk V, Baumgartner H, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery.* Oct 1 2017;52(4):616-664.
10. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* Jul 11 2017;70(2):252-289.
11. Feltes TF, Bacha E, Beekman RH, 3rd, et al. Indications for cardiac catheterization and intervention in pediatric cardiac disease: a scientific statement from the American Heart Association. *Circulation.* Jun 7 2011;123(22):2607-2652.
12. Badhwar V, Ofenloch JC, Rovin JD, van Gelder HM, Jacobs JP. Noninferiority of closely monitored mechanical valves to bioprostheses overshadowed by early mortality benefit in younger patients. *The Annals of Thoracic Surgery.* 2012;93(3):748-753.
13. Bernet FH, Baykut D, Grize L, Zerkowski H-R. Single-center outcome analysis of 1,161 patients with St. Jude medical and ATS open pivot mechanical heart valves. *The Journal of heart valve disease.* 2007;16(2):151-158.
14. Bourguignon T, Bergöend E, Mirza A, et al. Risk factors for valve-related complications after mechanical heart valve replacement in 505 patients with long-term follow up. *Journal of Heart Valve Disease.* 2011;20(6):673.
15. Chan V, Jamieson WE, Lam B-K, et al. Influence of the On-X mechanical prosthesis on intermediate-term major thromboembolism and hemorrhage: a prospective multicenter study. *The Journal of thoracic and cardiovascular surgery.* 2010;140(5):1053-1058. e1052.

16. Johnson S, Stroud MR, Kratz JM, Bradley SM, Crawford FA, Jr., Ikonomidis JS. Thirty-year experience with a bileaflet mechanical valve prosthesis. *Journal of Thoracic and Cardiovascular Surgery.* 2019-10-14 2019;157(1):213-222.
17. Minakata K, Tanaka S, Tamura N, et al. Comparison of the long-term outcomes of mechanical and bioprosthetic aortic valves: A propensity score analysis. *Circulation Journal.* 2017 2017;81(8):1198-1206.
18. Nishida T, Sonoda H, Oishi Y, et al. Long-term comparison of three types of aortic St. Jude Medical mechanical prosthesis in Japanese patients. *Circulation Journal.* 2015:CJ-15-0268.
19. Puskas J, Gerdisch M, Nichols D, et al. Reduced anticoagulation after mechanical aortic valve replacement: interim results from the prospective randomized on-X valve anticoagulation clinical trial randomized Food and Drug Administration investigational device exemption trial. *The Journal of thoracic and cardiovascular surgery.* 2014;147(4):1202-1211. e1202.
20. Van Nooten GJ, Bové T, Van Belleghem Y, et al. Twenty-year single-center experience with the medtronic open pivot mechanical heart valve. *The Annals of thoracic surgery.* 2014;97(4):1306-1313.
21. Kim SH, Kim HJ, Kim JB, et al. Supra-annular versus intra-annular prostheses in aortic valve replacement: impact on haemodynamics and clinical outcomes. *Interactive cardiovascular and thoracic surgery.* 2019;28(1):58-64.
22. Mostafa EA, El Midany AA, Taha AS, et al. On-X versus St Jude medical mechanical prosthesis in mitral position: Are we moving forward in design technology? *Journal of Cardiovascular Surgery.* 2018;59(2):252-258.
23. Prifti E, Bonacchi M, Minardi G, et al. Early and Mid-term Outcome of the St. Jude Medical Regent 19-mm Aortic Valve Mechanical Prosthesis. Functional and Haemodynamic Evaluation. *Heart, Lung and Circulation.* 2018;27(2):235-247.
24. Zhang H, Dong Y, Ao X, Zhu D, Dong L. Optimal oral anticoagulant therapy in Chinese patients with mechanical heart valves. *European Journal of Pharmaceutical Sciences.* 2020;144:105202.
25. Akins CW, Miller DC, Turina MI, et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. *European journal of cardio-thoracic surgery.* 2008;33(4):523-528.
26. Criteria Committe NYHAI. *Diseases of the Heart and Blood Vessels. Nomenclature and Criteria for Diagnosis.* 6th ed. Boston: Little, Brown and Co.; 1964.
27. Criteria Committe NYHAI. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. Boston, MA: Lippincott, Williams and Wilkins; 1994.
28. Peto R, Pike M, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. *British journal of cancer.* 1976;34(6):585-612.

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APPENDIX V: RATES OF FORSEEABLE ADVERSE EVENTS

[redacted]

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[redacted]

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APPENDIX VI: CASE REPORT FORMS

Case report forms will be provided under a separate cover.

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APPENDIX VII: INFORMED CONSENT FORM

Informed Consent Form (ICF) templates will be provided under a separate cover.

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APPENDIX VIII: MONITORING PLAN

A copy of the Monitoring Plan can be obtained upon request from the Sponsor Clinical Project Manager for the clinical investigation.

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APPENDIX IX: REVISION HISTORY

This CIP may be amended as appropriate by the Sponsor. Rationale will be included with each amended version in the revision history table below. The version number and date of amendments will be documented.

IRB/EC and relevant Regulatory Authorities, if applicable, will be notified of amendments to the CIP.

Amendment Number	Version	Date	Details	Rationale
[redacted]				

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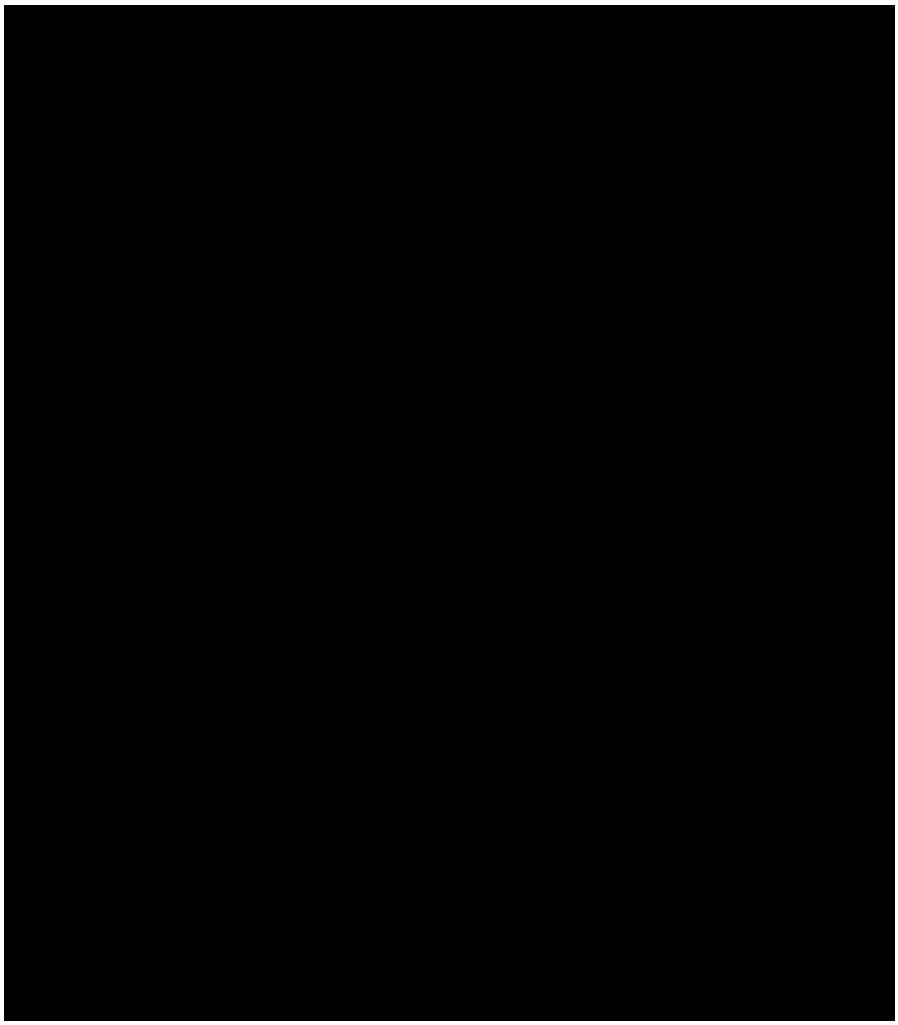

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APPENDIX X: CIP SUMMARY

Clinical Investigation Name and Number	RC-PMCF
Title	Regent China Post-Market Clinical Follow-up Study
Objective	Confirm the long-term safety and performance of Abbott Medical's Regent, model AGN-751 and AGFN-756, for replacement of native or prosthetic aortic valves.
Device Under Investigation	Abbott Medical's Regent Mechanical Heart Valve
Number of Subjects Required for Inclusion in Clinical Investigation	200
Clinical Investigation Design	Prospective, non-randomized, observational, multi-center study
Primary Endpoints	The primary safety endpoint is freedom from valve-related mortality at 5 years. The primary performance endpoint is freedom from valve-related reoperation at 5 years.
Subject Follow-up	Baseline, implant, discharge, 3-months, 6-months, and annually post-implant
Inclusion Criteria	1. Patient is eligible to be implanted with Regent to replace a native or prosthetic aortic valve per Regent MHV's IFU 2. Subject will be ≥18 years of age at time of being consented 3. Subject, provides written informed consent prior to any clinical investigation-specific procedure.
Exclusion Criteria	1. Subject is unable to tolerate anticoagulation therapy 2. Subject has active endocarditis 3. Subject is currently participating in another clinical investigation which may interfere with the effectiveness of anticoagulation therapy

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	4. Pregnant or nursing subjects and those who plan pregnancy during the clinical investigation follow-up period. Women of child-bearing potential must have a documented negative pregnancy test within one week prior to enrollment 5. Subject has anomalous anatomy or medical, surgical, psychological or social history or conditions that, in the Investigator's opinion, could limit the subject's ability to participate in the clinical investigation or to comply with follow-up requirements of the clinical investigation results 6. Subject is unable to read or write or has a mental illness or disability that impairs their ability to provide written informed consent 7. Subject's life expectancy is less than 1 year in the opinion of the Investigator