AcQBlate Force Sensing Ablation System US IDE for Atrial Flutter

(AcQForce Flutter)

Study CLP-21

23 September 2021

Rev 11

Acutus Medical, Inc

CONFIDENTIALITY STATEMENT

INVESTIGATOR PROTOCOL SIGNATURE PAGE AND AGREEMENT
CLP-21, Rev 11
I have read this Clinical Investigational Plan (CIP)/protocol and agree to adhere to all the requirements. The signature below constitutes the approval of the AcQForce Flutter CIP/protocol and provides assurances that this CIP/protocol will be conducted in accordance with all stipulations of the CIP/protocol including all statements regarding participant confidentiality. The AcQForce Flutter CIP/protocol will be followed in accordance with all national and local legal and regulatory requirements.

Site Investigator Printed Name

Site Investigator Signature

Date

dd-mmm-yyyy

REVISION HISTORY

Revision	Date	Description of Update	Reason for Update
01	05 May 2020	Initial release	N/A
02	27 July 2020	The following protocol edits were made to comply with FDA study considerations: • Revised pre-procedure TEE requirements based on anticoagulation history • Revised post-ablation anticoagulation requirement to include ≥ 4 weeks • Revised parameters/definitions for primary endpoint failure (includes catheter alternatives) • Revised sample size justification and calculation • Removed historical control as primary efficacy endpoint comparator • Revised the observational efficacy endpoint to be Class I & III AAD use both pre-and post-procedure • Revised AFL documentation (AFL with 12-lead ECG) • Clarified ablation parameters, and several statistical expectations for the study • Revised/updated clinical definitions for several safety events • Clarified anticoagulation recommendations (section 7.5.2) • Clarified and added language in section 7.5.3, 7.7.1, and 7.7.2	FDA Recommendation
03	25 September 2020	Update to section 7.7.1 Entrainment pacing Changes to power setting recommendations with a limitation of 30 W.	Internal review
04	01 March 2021	• Amendments to protocol to include the use of RF generator at power settings 31-50 watts. • Adjustments to protocol based on FDA feedback and recommendations.	FDA Recommendations and increase power setting to 50W max
05	22 April 2021	• Changes to power setting recommendations with limitation of 30W • Adjustments to protocol based on FDA feedback and recommendations	FDA Recommendation to include AcQMap, AcQTag, ATF Cable

		• Incorporated language on use of AcQMap, AcQTag	
06	04 May 2021	• Per FDA request, converted protocol to Rev 03 with the exception of the language on use of AcQMap and AcQTag	FDA requested changes
07	17 May 2021	• Per FDA request, converted protocol to Rev 03 • Clarified exclusion criteria #6 and #19, TTE and TEE requirements, atrial thrombus assessments • Adjusted sample size justification based on FDA feedback and recommendations	FDA and study site requested clarifications
08	01 July 2021	• Incorporated changes implemented in Rev 06 • Removed Rev 07 changes not approved by FDA	Combine FDA approved changes from Rev 06 and Rev 07
09	05 August 2021	• Incorporated use of RF generator at power settings 31-40 watts • Incorporated clarification on entrainment pacing requirements • Adjustments to protocol based on FDA study design considerations	Incorporate higher power setting, feedback from study sites and FDA recommendations
10	19 August 2021	• Increased study sites from 16 to 20	Internal review
11	23 September 2021	• Replaced Intent-to-Treat subject with Intent-to-Treat Failure Subject • Revised description of involved procedures in section 7.7.1	FDA Study Design Considerations

SPONSOR INFORMATION

Acutus Medical, Inc.
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1 CLINICAL STUDY SYNOPSIS

Study Title	AcQBlate Force Sensing Ablation System US IDE for Atrial Flutter (AcQForce Flutter)
Device Name	The AcQBlate Force Sensing Ablation System (herein known as the AcQBlate Force Sensing System) comprises the AcQBlate Force Sensing Ablation Catheter (AcQBlate® FORCE), the Qubic Force® Sensing Module (Qubic Force), the Qubic Radiofrequency (RF) Generator, and the Qiona Irrigation Pump with Tubing Set. The System is designed for electrophysiologic (EP) mapping and RF ablation of atrial flutter.
Study Device Components	The AcQBlate Force Sensing System comprises: • AcQBlate FORCE • Qubic Force • Qubic RF Generator • Qiona Irrigation Pump • Qiona Irrigation Tubing Set • Assorted Cables (for EP recording connectivity)
Indication for Use (Proposed)	The AcQBlate® FORCE Sensing Ablation Catheter and related accessory devices are indicated for cardiac electrophysiological mapping, delivery of diagnostic pacing stimuli, and radiofrequency ablation of recurrent and symptomatic atrial flutter (AFL) when used with a compatible RF Generator. When used with the Qubic Force® module, the AcQBlate® FORCE Sensing Ablation Catheter provides a real time measurement of contact force between the catheter tip and the heart.
Sponsor	Acutus Medical, Inc. 2210 Faraday Ave, Suite 100 Carlsbad, CA, USA 92008
Study Objective	The objective of the clinical study is to demonstrate the AcQBlate Force Sensing System is safe and effective when used to ablate the cavotricuspid isthmus (CTI) for the treatment of typical atrial flutter when compared to a literature-based control. Data will be used to support a pre-market approval (PMA) application.

Study Design	The Acutus Medical AcQForce Flutter clinical study is a prospective, multi-center, non-randomized global study designed to demonstrate the safety and effectiveness of the AcQBlate Force Sensing Ablation System in the ablation management of symptomatic cavotricuspid isthmus dependent atrial flutter. All subjects with typical atrial flutter will undergo percutaneous catheter ablation of the cavotricuspid isthmus using the AcQBlate Force Sensing System with the endpoint of achieving bidirectional block (BDB). Post procedural follow-up visits will be completed at pre-discharge, to assess device and procedure-related serious adverse events (SAEs), a 7-day phone call, and a 30-day clinic visit to assure compliance with all aspects of the study and report on the observational effectiveness endpoint. The expected safety and efficacy rates for the primary endpoints were derived from a meta-analysis of recently completed IDE trials). Event rates were estimated from Summary of Safety and Effectiveness Data (SSED) or results disclosed on *clinicaltrials.gov* and calculated based on the occurrence of events that constitute the primary safety and efficacy endpoints defined in this protocol.
Patient Population	Subjects 18 years and older, presenting for a *de novo* percutaneous cardiac ablation of the cavotricuspid isthmus for typical atrial flutter will be included in the AcQForce Flutter study.
Primary Safety Endpoint	The Primary Safety Endpoint for the AcQForce Flutter study is a comparative analysis of subjects free from a composite list of pre-specified procedure/device related Serious Adverse Events (SAEs) through 7-days post ablation using a literature-based control. Serious Adverse Events are pre-defined and include: • Death • Cardiac tamponade/perforation • Myocardial infarction • Stroke • Systemic embolism • Major access site complications • Major bleeding requiring transfusion • Complete heart block • Other SAEs/SADEs adjudicated by an independent review as “probably or definitely related” to the Investigational device.

Primary Effectiveness Endpoint	The Primary Effectiveness Endpoint for the AcQForce Flutter study is an analysis of subjects achieving acute procedural success. Acute procedural success is defined as the demonstration of bidirectional cavotricuspid isthmus block at least 20 minutes following the last radiofrequency application at the cavotricuspid isthmus with the investigational System. Bidirectional block (BDB) confirmation is defined as: • Demonstration of bidirectional electrophysiological conduction block through the cavotricuspid isthmus (CTI) using both coronary sinus ostium (CS) and annular low right atrial pacing maneuvers.
Observational Effectiveness Endpoint	Freedom from recurrence of typical CTI dependent atrial flutter OFF Class I/III antiarrhythmic drugs (AADs) at 30-days post index procedure as measured by a 24-hour continuous electrocardiogram (ECG) monitor.
Study Sample Size	The sample size consists of 110 Modified Intent-to-Treat (mITT) subjects, based on using a one-sided α of 0.05, with 90% power. A maximum of 120 Modified Intent-to-Treat (mITT) subjects will be enrolled. mITT subjects are any enrolled subjects who initiate the ablation procedure using the AcQBlate Force Sensing System.
Study Geographies	The AcQForce Flutter Study will be conducted at up to 20 clinical study sites in the USA and Europe.
Study Duration	The clinical study is anticipated to take approximately 12-months to enroll and will include a 30-day follow-up period. Total clinical study duration is anticipated to be approximately 12-18 months. The per patient clinical study duration is expected to be approximately six (6) weeks.

Inclusion Criteria	A potential study subject will meet all the following inclusion criteria: 1. Subjects are clinically indicated for *de novo* catheter ablation of typical atrial flutter. 2. At least one (1) documented episode of typical atrial flutter within 180 days (6 months) prior to enrollment, documented by 12-lead ECG. 3. Age 18 years or older at time of consent. 4. Subjects are willing and able to provide written informed consent to participate in the study and agree to comply with all follow-up visits and evaluations.
Exclusion Criteria	A potential study subject who meets any of the following exclusion criteria will be excluded: 1. In the opinion of the Investigator, any contraindication to the planned atrial ablation, including contraindications to anticoagulation therapy and any other significant uncontrolled or unstable medical condition (e.g. sepsis, acute metabolic illness, chronic kidney disease). 2. Inability to document cavotricuspid isthmus conduction. 3. Any prior right atrial cavotricuspid isthmus ablation. 4. Any cardiac ablation for non-atrial flutter arrhythmias within 90 days prior to enrollment. 5. Any patient scheduled or anticipating an AF ablation within the follow-up period. 6. Administration of oral amiodarone within 120 days prior to procedure excluding a one-time IV/oral administration of ≤ 2000 mg in a 24-hour period. 7. Cardiac surgery within 60 days prior to enrollment. 8. ST-elevation myocardial infarction (STEMI) within 60 days prior to enrollment 9. Current unstable angina. 10. Documented atrial or ventricular tumors, clots, thrombus, within 30-days prior to enrollment. 11. Any history of a known hematologic disorder (bleeding/clotting). 12. Implantation of permanent leads of an implantable device in or through the right atrium within 90-days prior to enrollment. 13. Subjects with New York Heart Association (NYHA) Class IV heart failure within 6-months prior to enrollment. 14. Subjects with an ejection fraction less than 30% within 90 days of

	enrollment. 15. Percutaneous Transluminal Coronary Angioplasty (PTCA) within 30-days of enrollment. 16. Clinically significant structural heart disease (including moderate to severe tricuspid valve regurgitation, tricuspid valve stenosis, or tricuspid valve replacement; Ebstein's anomaly, or other congenital heart disease) that would preclude catheter introduction and placement, as determined by the Investigator. 17. Any cerebral ischemic/infarct event (excluding transient ischemic attacks) within 180 days prior to enrollment. 18. Body Mass Index (BMI) >42 kg/m^2. 19. International Normalized Ratio (INR) > 3 (required for patients taking warfarin). 20. Severe uncontrolled systemic hypertension (systolic pressure > 240 mm Hg) within the last 30-days. 21. Women who are pregnant or plan to become pregnant within the course of their participation in the investigation. 22. Current enrollment in any other study protocol where testing or results from the study may interfere with the procedure or outcome measurements for this study. 23. Any other condition that, in the judgment of the Investigator, makes the patient a poor candidate for this procedure, the study or compliance with the protocol (includes vulnerable patient population, mental illness, addictive disease, terminal illness with a life expectancy of less than two years, extensive travel away from the research center).
Statistical Analysis	A comparative assessment of the safety and effectiveness of the AcQBlate Force Sensing System will be made with findings reported in the literature for a similar patient population. Sample size calculations are based on a literature-based control for the composite SAE and efficacy rates for catheter ablation of typical atrial flutter.

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2 ABBREVIATIONS

3D	Three-Dimensional
AADs	Antiarrhythmic Drugs
ACC	American College of Cardiology
ADE	Adverse Device Effect
AE	Adverse Event
AF	Atrial Fibrillation
AFL	Atrial Flutter
AHA	American Heart Association
ARDS	Acute Respiratory Distress Syndrome
AT	Atrial Tachycardia
Au	Gold
AV	Atrioventricular/Arteriovenous
BDB	Bidirectional Block
BMI	Body Mass Index
CA	Competent Authority
CF	Contact Force
CFR	Code of Federal Regulations
CIP	Clinical Investigational Plan
CL	Cycle Length
CMP	Clinical Monitoring Plan
COR	Classification of Recommendation
CRA	Clinical Research Associate
CRO	Contract Research Organization
CS	Coronary Sinus
CSR	Clinical Study Report
CT	Computed Tomography
CTI	Cavotricuspid Isthmus
DCCV	Direct Current Cardioversion
DD	Device Deficiency
DMP	Data Management Plan
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EP	Electrophysiology/Electrophysiological
eCRF	Electronic Case Report Form
FBG	Fiber Bragg Grating
FDA	Food and Drug Administration
FTI	Force Time Integral

G	Grams
Gs	Gram second
GCP	Good Clinical Practices
GDPR	General Data Protection Regulation
eGFR	Estimated Glomerular Filtration Rate
HCP	Health Care Professional
HRS	Heart Rhythm Society
IA	Investigator Agreement
ICE	Intracardiac Echocardiogram
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IEGM	Intracardiac Electrogram
IFU	Instructions For Use
INR	International Normalized Ratio
IRB	Institutional Review Board
ISF	Investigator Site File
ISO	International Organization for Standardization
ITT	Intent-to-Treat Failure
IVC	Inferior Vena Cava
LBBB	Left Bundle Branch Block
LA	Left Atrium/Left Atrial
LFU	Lost to Follow-up
LOE	Level of Evidence
mITT	Modified Intent-to-Treat
mm	Millimeter
MRI	Magnetic Resonance Imaging
NaCl	Normal Saline
NYHA	New York Heart Association
OM	Operator Manual
PAF	Paroxysmal Atrial Fibrillation
PI	Principal Investigator
PMA	Pre-Market Approval
PPT	Pre-procedure Testing Failure
PTCA	Percutaneous Transluminal Coronary Angioplasty
PtIr	Platinum Iridium
PV	Pulmonary Vein
PVI	Pulmonary Vein Isolation
QAP	Quality Assurance Procedure
RA	Right Atrium/Right Atrial
RF	Radiofrequency

RFA	Radiofrequency Ablation
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SIV	Site Initiation Visit
SOC	Standard of Care
SQV	Site Qualification Visit
SR	Sinus Rhythm
SSED	Summary of Safety and Effectiveness Data
SVT	Supraventricular Tachycardia
TA	Tricuspid Annulus
TEE	Transesophageal Echocardiogram
TIA	Transient Ischemic Attack
TMF	Trial Master File
TTE	Transthoracic Echocardiogram
UADE	Unanticipated Adverse Device Effect
W	Watts

3 INTRODUCTION

3.1 Background

Atrial Flutter

Atrial flutter (AFL) is a macroreentrant atrial arrhythmia typified by regular atrial contractions between 250 and 350 beats per minute, a constant P-wave morphology, and a 2:1 atrial to ventricular conduction.[1,2] Atrial flutter, while being a common arrythmia, can cause significant symptoms (palpitations, shortness of breath, dizziness or fainting) and sequelae. The hemodynamic condition of the patient determines whether immediate cardioversion to sinus rhythm (SR) is attempted. Endocardial mapping suggests that typical atrial flutter is based on right atrial macro reentry which involves the isthmus between the inferior vena cava (IVC) and the tricuspid annulus (TA). An atrial flutter circuit that is dependent on conduction through the cavotricuspid isthmus (CTI) is designated CTI-dependent atrial flutter. A flutter involving a circuit that wraps around the tricuspid valve in a counter clockwise fashion is termed "typical" AFL, while a circuit rotates in a clockwise fashion is called "clockwise or reverse typical" AFL.[1,3] In typical AFL, the flutter waves are negative in leads II and III and positive in lead V_1.[2]

Atrial flutter is a relatively common arrhythmia. The overall incidence of atrial flutter is estimated to be 0.088% (or 88 per 100,000 people).[4] The incidence is 2.5 times higher in men than in women, and increases with age. Over one-half of these patients with atrial flutter also have atrial fibrillation (AF). Atrial flutter can be triggered by atrial tachycardia (AT) or atrial fibrillation (AF). Atrial flutter alone is seen in 0.037% of the population. The incidence of atrial flutter increased markedly with age, from 5 per 100,000 of those older than 50 years of age to 587 per 100,000 for those older than 80 years of age. The incidence of atrial flutter has been reported to be approximately twice that of paroxysmal supraventricular tachycardia.[2,5] According to the American Heart Association (AHA) guidelines, the risks of thrombo-embolic events due to atrial flutter, including strokes, is the same as that for atrial fibrillation, therefore recommendations for anticoagulation therapy should be similar to those for subjects with AF.[6,7,8]

Current Therapies for Atrial Flutter

Current treatments offer non-invasive and invasive options which include pharmaceutical and ablation catheter-based approaches.[7] Since 2003, the FDA has approved premarket approval (PMA) applications for ablation catheter systems indicated for the treatment of atrial flutter. The American College of Cardiology (ACC) and the American Heart Association (AHA Task Force) has applied a Classification of Recommendation (COR) and Level of Evidence (LOE) for cavotricuspid isthmus catheter-based ablation for symptomatic or drug refractory AFL of COR I and LOE B.[7] Catheter ablation of typical AFL has been shown to be highly effective with an acute procedural success rate that in some studies may be as high as 97%.[9] A systematic review and meta-analysis evaluating the safety and efficacy

of radiofrequency ablation (RFA) of typical AFL demonstrated a single-procedure acute success rate for AFL at 91.7% (95% CI: 88.4%-94.9%). Multiple-procedure success was 97.0% (95% CI: 94.7%-99.4%). Post-ablation arrhythmia was noted in 13.2% of subjects (95% CI: 7.5% -18.9%), while repeat ablation was reported in 8% (95% CI: 4.5%-11.4%). Reported all-cause mortality has been relatively low in AFL studies (<1%), while serious adverse event rates up to 9% have been reported in clinical studies supporting PMA applications. Studies of radiofrequency ablation for the treatment of AFL and supraventricular tachycardia (SVT) report high efficacy rates and relatively low rates of major complications.[9]

Among the various physical principles applied to catheter ablation, the application of RF energy is the most widespread technology. Alternative types of ablation energy include cryo-ablation, laser ablation, and ultrasound ablation. During the process of RF ablation electromagnetic energy is transformed into thermal energy, whereby the process of resistive heating destroys cardiac tissue, modifying the electrical properties of the tissue, establishing electrical isolation of arrhythmic triggers or circuits.[10] Currently, RF ablation is considered first-line therapy for treatment of AFL. Lesion formation created during RF catheter ablation of the CTI depends on multiple factors: power delivery, duration of the energy applied, tissue temperature, atrial anatomy, ablation catheter tip size and orientation.[11] Success of AFL ablation is highly influenced by CTI length and morphology, to perhaps a greater degree than choice of catheter tip. Da Costa, et al., evaluated the role of CTI anatomy in the ability to achieve acute and chronic procedural success. An 8 millimeter (mm) tip catheter was more effective than an irrigated catheter in straight isthmus anatomy, while ablation efficacy was increased with an irrigated tip catheter in concave isthmus morphologies.[12] The depth of the sub-Eustachian pouch has been shown to be the sole factor that influenced RF duration and energy during a CTI ablation often necessitating the deflection of the catheter by more than 90 degrees to ablate within the pouch (knuckle-curve ablation).[13] Achieving lesion transmurality, i.e., lesions that extend the full thickness along the 1-6 centimeter (cm) of the isthmus, is essential for the continuity and durability of catheter ablation success.[14] By employing catheters which improve the electrode-tissue interface, the transfer of thermal energy to the cardiac tissue is enhanced.[10]

Contact Force Technology

Contact force (CF) catheter technology provides real-time sensing of catheter-to-tissue pressure enabling the appropriate delivery of RF energy to the endocardial surface. The distal tip of a contact force catheter houses a force sensing mechanism, providing real-time assessment of catheter-tissue contact.[15] With improved electrode-tissue contact the transfer of thermal energy to the tissue is maximized. When contact force is increased the proportion of the electrode surface in contact with the endocardium is enhanced. Further, by increasing catheter-tissue contact, lesion size, volume, and depth are increased.[16,17,18] Animal models suggest that the optimal contact force required to make transmural lesions is between 10

grams (g) and 20 g.[19] These findings have been similarly represented with human data.[20] The benefits of contact force sensing were initially demonstrated by the TOCCATA (NCT01223469) study which evaluated the safety and effectiveness of the real-time CF sensing using the TactiCath catheter in 77 subjects treated for right sided supraventricular tachycardias (SVT) and paroxysmal atrial fibrillation (PAF).[21] From this initial study it was identified that a mean contact force of > 20 g was associated with an 80% probability of being in sinus rhythm 12-months following an index ablation. Results from multiple studies have demonstrated that using optimal contact force improves mid to long term AF ablation success rates and reduces arrhythmia recurrence rates when CF sensing catheters were compared to a non-CF sensing catheters.[20,22,23] The TOCCASTAR study established that the atrial arrhythmia free rate was significantly higher when a minimum of ≥ 10 g was applied to ≥ 90% of the ablation lesions, confirming that optimal contact force is associated with improved effectiveness.[20]

While the use of contact force is well established for pulmonary vein isolation (PVI), there is limited information regarding its utility in CTI ablation. CTI ablation creates unique challenges given the anatomy of the CTI is non-uniform, exhibiting decreasing tissue density when transitioning from the tricuspid annulus to the vena cava. Additionally, the presence of the Eustachian ridge, sub-Eustastian pouches, or pectinate muscle may limit the ability to create adequate lesions and may benefit from contact force. While low contact force (< 10 g) during PVI has been shown to be a play a critical role in lesion size and has been identified as a predictor of acute and chronic PVI reconnection, a similar association was lacking for CTI ablation. Kumar et al., examined the effect of varying anatomy on levels of contact force achieved during CTI ablation. The CTI was divided into equal length segments; annular, mid, and caval. The annular isthmus corresponded to the vestibule leading to the tricuspid valve, while the caval segment was closest to the orifice of the inferior vena cava, containing the Eustachian ridge. Wide variations in CF were observed within and between CTI regions. The highest CF was recorded in the caval region, followed by mid and annular sections. Low contact force was correlated with an increase in both the total ablation time to achieve bidirectional block and acute reconnection. The majority of reconnections observed during the 30 minute post ablation waiting period were in the mid-CTI region (54%).[24] Verner et. al., found an inverse correlation between RF delivery and the percent of lesions delivered > 10 g, with total RF time significantly increased with lesions < 10 g.[25] Use of a detectible long vascular sheath has been suggested to achieve CF catheter stability along the CTI, improve maneuverability, thereby enhancing CF.[23,24]

When comparing the performance of ablation catheter types, a recent study evaluated the acute efficacy of a CF catheter and a non-CF catheter with the endpoint of achieving bidirectional block.[26] Catheter ablation using a CF catheter achieved acute bidirectional block in 100% of patients while only 90% of non-CF catheter ablations met the endpoint of bidirectional block. The authors suggest CF parameters may help overcome potential anatomical difficulties.[26] The recent analysis of the safety and effectiveness of an irrigated,

gold tipped contact force catheter (AlCath Force catheter equivalent to AcQBlate FORCE) for subjects indicated for CTI and PAF ablation demonstrated acute procedural success (bidirectional block) with a mean contact force of 25.6 ± 7.3 g. Detailed results are provided in section 4.

3.2 Justification for Investigation and Study Design

Catheter ablation of the cavotricuspid isthmus has been a therapeutic mainstay for the treatment of typical atrial flutter for the past decade. The current understanding of the field of catheter ablation makes for a mature marketplace of irrigated, non-irrigated, and contact force catheters for CTI ablation. The intended use and intended use population of the AcQBlate® FORCE is identical to those of current RF ablation catheters from other manufacturers approved for the ablation of atrial flutter.

The expected safety rates for the primary safety and efficacy endpoints were derived from a meta-analysis of recently completed IDE trials and publications related to the safety and efficacy of typical CTI dependent atrial flutter ablation (see Table 1). Event rates were estimated from Summary of Safety and Effectiveness Data (SSED), results disclosed on *clinicaltrials.gov*, peer reviewed publications. and were calculated based on the occurrence of events that constitute the primary safety and efficacy endpoints defined in this protocol.

Table 1. Meta-Analysis to Determine Sample Size for Efficacy

Device Trade Name (PMA Number)	Month/Year	n	Efficacy Estimate**
NaviStar™ DS 8 mm Deflectable Diagnostic Ablation Catheter Celsius™ DS 8 mm Deflectable Diagnostic Ablation Catheter Stockert 70 RF Generator (model 87001 with software version 001/033) Catheter Interface Cables (models D-1195 and D-1170) (P010068)	09/2002	182	90.1%
IBI Therapy™ Dual8 ™ Ablation Catheter IBI-1500T6 (USA) Cardiac Ablation Generator (P040042)	11/2005	150	93.3%
Therapy Cool Path Duo™ Ablation Catheter Safire BLU Duo™ Ablation Catheter 1500T9-CP Vi.6 Cardiac Ablation Generator (P110016)	01/2012	188	96.3%
Therapy™ Cool Flex™ Ablation Catheter (P110016/ S008)	12/2013	179	98.9%
Blazer® Open-Irrigated Ablation Catheter Maestro 4000™ Cardiac Ablation System MetriQ™ Irrigation Pump MetriQ™ Irrigation Tubing Set (P150005)	02/2016	109	87.2%
		Mean	**93.2%**
		Weighted Mean	**93.7%**

**Bidirectional CTI Block 30-60 minutes following last RF ablation.

Of the SSEDs listed in Table 1, none provided a comprehensive, tabular summary of SAEs that corresponds with the composite list used for the statistical analysis of the primary safety endpoint of the AcQForce Flutter clinical study. The TOCCATTA trial[21] was the first multicenter, randomized, controlled trial that used direct contact force in human subjects. The overall event rate for right sided ablations was 2.3%. A comparison of reported events within the SSEDs and the TOCCATTA trial to the pre-defined composite safety definitions suggests an approximate SAE mean event rate of 3.0%, and a weighted mean of 2.9% (Table 2). Note that rates reported in individual studies varied between 2.1% and 5.3%. To account for any differences between the AcQForce Flutter study's primary safety endpoint compared to the previous studies used in the meta-analysis, a derived safety event rate of 3% is expected. Based on this, a performance goal is proposed based on an expected rate of 98.5% and a 5.5% statistical margin. This will define the safety population sample size to support a primary safety endpoint with at least 90% power for the planned sample size.

Table 2. Estimated Safety Event Rate Based on Pre-defined Serious Adverse Events

		Acutus Pre-defined SAE								
Device Trade Name (PMA Number)	**N**	**Death**	**Cardiac perforation / Pericardial Tamponade**	**Cerebral Infarct or Systemic Embolism**	**Myocardial Infarct**	**Major Access Site Complication**	**Major Bleeding requiring transfusion**	**Complete Heart Block**	**Other Device related SAEs / SADEs**	**Estimated Safety Event Rate**
NaviStar™ DS 8 mm Deflectable Diagnostic Ablation Catheter Celsius™ DS 8 mm Deflectable Diagnostic Ablation Catheter Stockert 70 RF Generator (model 87001 with software version 001/033) Catheter Interface Cables (models D-1195 and D-1170) (P010068)	182	Not Specified	Not Specified	Not Specified	Not Specified	1 (0.5%)	Not Specified	1 (0.5%)	2 (1.1%)	**2.2%**
IBI Therapyr™ Dual 8 ™ Ablation Catheter IBI-1500T6 (USA) Cardiac Ablation Generator (P040042)	150	Not Specified	Not Specified	Not Specified	1 (0.6%)	Not Specified	Not Specified	Not Specified	7 (4.7)	**5.3%**
Therapy Cool Path Duo™ Ablation Catheter Safire BLU Duo™ Ablation Catheter 1500T9-CP Vi.6 Cardiac Ablation Generator (P110016)	188	1 (0.5%)	Not Specified	Not Specified	Not Specified	Not Specified	Not Specified	Not Specified	3 (1.6%)	**2.1%**
Therapy™ Cool Flex™ Ablation Catheter (P110016/ S008)	179	1 (0.6%)	Not Specified	1 (0.6%)	Not Specified	Not Specified	Not Specified	Not Specified	2 (1.1%)	**2.2%**
Blazer® Open-Irrigated Ablation Catheter Maestro 4000™ Cardiac Ablation System MetriQ™ Irrigation Pump MetriQ™ Irrigation Tubing Set (P150005)	109	Not Specified	1 (0.9%)	1 (0.9%)	Not Specified	1 (0.9%)	Not Specified	Not Specified	0 (0.0%)	**2.8%**
TOCCATTA[20] (NCT01223469)	152	Not Specified	2 (1.3%)	Not Specified	Not Specified	3 (2.0%)	Not Specified	Not Specified	Not Specified	**3.3%**
									Average	**3.0%**
									Weighted Average	**2.9%**

The overall acute efficacy rate from this meta-analysis is 93.7%. Of the five studies evaluated, all studies passed their pre-specified acute efficacy endpoint establishing an acceptable procedural efficacy profile for the catheter under evaluation. A performance goal, using a weighted mean based on sample size, was derived from the meta-analysis. The resultant efficacy performance goal with a 10% statistical margin is 83.7%.

The Primary Safety endpoint of subjects free from a pre-specified composite list of procedure/device related Serious Adverse Events through 7-days post ablation using a literature based control comparative analysis will drive the sample size. A maximum of 110 mITT subjects* will be enrolled based on a one sided α 0.05, 90% power, and a 5.5% statistical margin. For the purposes of this study a maximum of 110 patients will be enrolled at twenty sites.

The following assumptions were used in the calculation of sample size:

Endpoint	Literature Based Control	Statistical Margin	Performance Goal	Acutus Estimate	90% Power α 0.050
Primary Safety	97%	5.5%	93%	98.5%	110*
Primary Efficacy	93.7%	10%	83.7%	93.7%	85

Inherent limitations in single arm design will be mitigated by limiting bias and confounders in the protocol, including inclusion/exclusion criteria similar to the trials comprising the meta-analysis, as well as rigorous patient screening and arrhythmia recurrence monitoring.

4 REPORT OF PRIOR INVESTIGATIONS

4.1 Overview

In May of 2019, Acutus Medical, via a joint agreement, acquired the Biotronik AlCath Force Sensing Catheter and Qubic Force Sensing Module technology. The AlCath Force catheter was rebranded as the AcQBlate Force Sensing Ablation Catheter and manufacturing was moved to Carlsbad, California. The Qubic Force Sensing Module retained its initial branding.

Following CE Mark approval, Biotronik conducted the post-market, prospective, BIO|CONCEPT AlCath Force study enrolling 30 subjects with PAF and/or typical AFL at 6 sites in Australia. Ablation procedure included PVI only (n=12), CTI only (n=16), and PVI plus CTI (n=2). The study objective was to provide continued clinical evidence supporting the safety and efficacy of the devices and identify additional risks associated with use. Safety endpoints included the collection of all SAEs and serious adverse device effects (SADEs)

through procedure discharge. The efficacy endpoint was the determination of electrical isolation defined as PV isolation for the pulmonary vein (PV) ablation and bidirectional block for the CTI ablations.

4.2 AlCath Force Ablation Procedure

Electrophysiological examinations during the ablation procedure were performed according to clinical study site preference for PVI and CTI ablations. The AlCath Force catheter and Qubic Force were operated as labeled. Target values for contact force, contact force ranges, and force time integrals (FTI) were at the discretion of the Investigator. The following recommendations were adhered to:

- Maximum tip temperature: 42° C (mandatory).
- Energy delivery ≤ FTI of 450 gram seconds (gs) in any catheter position.
- Initial power titration of energy ≤ 25 W. After 15 seconds, the energy could be increased until a transmural lesion was achieved.
- When ablating the posterior wall, a reduction in power and FTI was recommended.
- Irrigation flow rates during mapping and ablation followed the Instructions for Use (IFU).

4.3 Results

Baseline demographics are reported in the Table 3 below:

Table 3: BIOCONCEPT AlCath Force Baseline Demographics and Co-Morbidities

Characteristic	**Mean ± SD**
Gender	Male 23 Female 7
Age	64.7 ± 10.7
Weight (kg)	93.7 ± 17
BMI	30.3 ± 4.8
Systolic BP	142.1 ± 15.9
Diastolic BP	76.5 ± 12.9
Co-Morbidities	Frequency (%)
Ischemic heart disease	5 (16.7)

Hypertension	17 (56.7)
Asthma or chronic lung disease (except COPD)	4 (13.3)
Peripheral vascular disease	2 (6.7)
Diabetes Mellitus	8 (26.7)
Renal dysfunction/chronic renal disease	5 (16.7)
COPD (chronic obstructive pulmonary disease)	5 (16.7)

Severe Adverse Device Effects (SADE)

No deaths or SADEs were reported throughout the duration of the clinical study.

Acute Procedural Success

Acute procedural success was defined as isolation of all four pulmonary veins with demonstrated entrance and exit block in subjects receiving an ablation for AF. Fourteen subjects treated for AF demonstrated acute procedural success (14/14, 100%). For subjects receiving a CTI ablation, acute procedural success was defined as bidirectional block across the cavotricuspid isthmus with conformation via differential pacing. Seventeen subjects (17/18 94.4%) achieved the procedure endpoint.

Device Performance

A total of 38 catheters were used in the 30 procedures. Six device deficiencies were observed (6/38, 15.8%). Three of the device deficiencies required the crossover to another AlCath Force catheter. No device deficiencies were noted with the Qubic Force.

A total of 56 usability parameters were assessed: 27 parameters for the AlCath Force catheter and 29 parameters for the Qubic Force. The assessment of usability of the AlCath Force catheter and Qubic Force was positive with 99% of usability aspects rated as “adequate”, “good”, or “very good”. Approximately 1% of rates were ranked as “poor” or “very poor”.

Ablation parameters for the PVI and CTI ablations are outlined in the Table 4 below:

Table 4: BIOCONCEPT AlCath Force Procedure Parameters during RF Ablation

Variable	Subgroup (n)*	Data Mean ± SD (min, max)
High Rate Irrigation Flow Setting (ml)	CTI Ablation (16)	17.5 ± 3.6 (12, 30)
	PVI Ablation (12)	19.2 ± 5.1 (17, 30)

Variable	Subgroup (n)*	Data Mean ± SD (min, max)
	CTI plus PVI (2)	17.0 ± 0 (17, 17)
	All (30)	18.1 ± 4.1 (12, 30)
Low Rate Irrigation Flow Setting (ml)	CTI Ablation	2.0 ± 0 (2, 2)
	PVI Ablation	2.2 ± 0.6 (2, 4)
	CTI plus PVI	2.0 ± 0 (2, 2)
	All	2.1 ± 0.4 (2, 4)
Cumulative Irrigation Volume (ml)	CTI Ablation	519 ± 267 (174, 1100)
	PVI Ablation	892 ± 441 (340, 1950)
	CTI plus PVI	765 ± 101 (694, 837)
	All	684 ± 380 (174, 1950)
Pre-set RF Power (W)	CTI Ablation	30 ± 0 (30, 30)
	PVI Ablation	22.9 ± 4.5 (20, 30)
	CTI plus PVI	30 ± 0 (30, 30)
	All	27.2 ± 4.5 (20, 30)
Maximum RF Power (W)	CTI Ablation	31.3 ± 3.4 (30, 40)
	PVI Ablation	27.5 ± 2.6 (25, 30)
	CTI plus PVI	30 ± 0 (30, 30)
	All	29.7 ± 3.5 (25, 40)

Variable	Subgroup (n)*	Data Mean ± SD (min, max)
Maximum Tip Temperature Reached (C°)	CTI Ablation	36.4 ± 3 (31, 42)
	PVI Ablation	34.9 ± 2 (33, 39)
	CTI plus PVI	38.5 ± 4.9 (35, 42)
	All	35.9 ± 2.8 (31, 42)
Cumulative Duration of Energy Delivery (min)	CTI Ablation	22.1 ± 12.5 (4, 51)
	PVI Ablation	46.1 ± 21.4 (19, 97)
	CTI plus PVI	39.5 ± 4.9 (36, 43)
Aimed Contact Force (g)	CTI Ablation	25.6 ± 7.3 (7.3, 20)
	PVI Ablation	25.0 ± 8.0 (8.0, 20)
	CTI plus PVI	30.0 ± 0 (30, 30)
	All	25.0 ± 7.3 (20, 40)

*N values remain the same for all subgroups

Protocol Deviations

Protocol related deviations were observed in four subjects, including an application of RF power > 40 W (n=2), a minor infraction to the informed consent process, and the enrollment of a subject not eligible based on inclusion/exclusion criteria.

4.4 Conclusions

The BIO|CONCEPT AlCath Force post-market clinical study demonstrated the AlCath Force Sensing Ablation Catheter and the Qubic Force Sensing Module were safe and effective. Although a small sample size was studied, no serious adverse device effects were noted. Acute outcomes were 100% and 94.4% for the AF and AFL populations, respectively. The clinical study did not evaluate long-term arrhythmia management effectiveness.

5 STUDY DEVICE DESCRIPTION

5.1 Indication for Use (proposed)

The AcQBlate® FORCE Sensing Ablation Catheter and related accessory devices are indicated for cardiac electrophysiological mapping, delivery of diagnostic pacing stimuli, and radiofrequency ablation of recurrent and symptomatic atrial flutter (AFL) when used with a compatible RF Generator. When used with the Qubic Force® module, the AcQBlate® FORCE Sensing Ablation Catheter provides a real time measurement of contact force between the catheter tip and the heart.

5.2 AcQBlate® Force Sensing Ablation System

The AcQBlate® Force Sensing Ablation System (herein known as AcQBlate Force Sensing System) comprises the AcQBlate Force Sensing Ablation Catheter (AcQBlate® FORCE), the Qubic Force Sensing Module (Qubic Force), the Qubic RF Generator, and the Qiona Irrigation Pump with Tubing Set. The System is designed for EP mapping and RF ablation of typical atrial flutter.

5.3 AcQBlate Force Sensing Ablation Catheter

The AcQBlate Force is a unidirectionally deflectable, steerable, quadripolar, irrigated ablation catheter with an integrated force sensor for intracardiac application. It is designed for EP mapping and RF ablation of cardiac arrhythmias.

5.3.1 Qubic Force Sensing Module

The AcQBlate FORCE contact force monitoring capability requires connection with the Qubic Force Sensing Module (Qubic Force) by means of an optical cable which is permanently attached to the catheter.

The Qubic Force is a non-sterile, reusable unit that does not contact the patient . It processes the contact force signal from the AcQBlate FORCE during an EP procedure irrespective of an RF energy application (ablation).

5.4 Qubic Radiofrequency (RF) Generator

The Qubic RF Generator is a modular RF generator that can be used in combination with the AcQBlate FORCE for cardiac RF ablation. The values measured during ablation are shown on the display and control unit screen.

5.5 Qiona Irrigation Pump and Tubing Set

The Qiona Ablation Irrigation Pump is used in conjunction with a tubing set to deliver a sterile 0.9% sodium chloride solution (normal saline) for the purpose of cooling the AlCath Flux catheter tip during ablation procedures.

5.6 The AcQBlate Force System Operation

General

Equipment used during an EP procedure may include devices for introduction of the catheter into the vascular system, catheter visualization, processing the EP signals, and devices providing electrical stimulation for diagnostic purposes. In this clinical study, the AcQBlate FORCE catheter will be used with the Qubic Force, the Qubic RF Generator and the Qiona Ablation Irrigation Pump with Tubing Set . These devices are not FDA approved and therefore considered investigational devices.

In a typical ablation procedure, EP mapping is performed to identify and map the arrhythmogenic areas in the heart to be targeted for subsequent ablation. All catheter manipulations during mapping and ablation should be performed with a navigational guidance (fluoroscopic, intracardiac echo and/or 3D navigation devices).

Electrophysiologic Mapping

Prior to the actual ablation, diagnostic EP mapping may be performed with the AcQBlate FORCE. During this process, the contact force information provided by the Qubic Force may be used to monitor the contact between the catheter tip and the myocardial tissue and may assist the operator to obtain stable intracardiac signals of appropriate quality. Moreover,

contact force monitoring may reduce the risk of cardiac perforation as a result of excessive contact force. During EP mapping the electrodes of the AcQBlate FORCE can be used for pacing. Procedures and routines used during the mapping procedure strongly depend on the arrhythmia(s) to be treated.

Advanced Mapping Systems

The AcQBlate Force System is compatible with the Acutus Medical AcQMap System with investigational frame software v3.6.4.XX. Use of the AcQMap System with the investigational frame software may be utilized to support display of ablation parameters. The ablation specific data includes the below listed parameters:

- Contact force from Qubic Force
- Power from Qubic RF
- AcQTag – used to color and size markers automatically on the 3D anatomy model
- Listing of generic auxiliary catheters

The AcQMap System with the investigational frame software is considered part of the investigational device and is an optional accessory to the AcQBlate Force System. Use of the AcQMap System with investigational frame software v3.6.4.XX should be at the discretion of the Investigator.

RF Ablation

Once the targets for ablation have been appropriately identified, ablation is performed using the AcQBlate FORCE ablation functionality. The ablation electrode at the tip of the catheter is positioned by means of the steering mechanism on the proximal handle and RF current is applied by the Qubic RF generator. RF application is a functionality of the Qubic RF generator, not directly controlled by the AcQBlate FORCE catheter. Irrigated ablation catheters like the AcQBlate FORCE are used in power-controlled mode. In this mode, the supply of RF current is regulated and/or discontinued if the power exceeds a user-defined threshold. Additionally, a temperature cut-off is set to define a maximum catheter tip temperature to stop RF delivery in case of overheat. This may reduce the risk of steam pops and cardiac perforation as well as prevent excessive scar formation and thermal coagulation of blood at the ablation site.

The contact force shown by the Qubic Force is an indication of the quality of the contact between the ablation electrode and the myocardial tissue. The operator may use the contact force information to monitor the tissue-electrode contact and achieve effective lesion creation while minimizing the risk of cardiac perforation. The direction of the total contact force vector indicated by the Qubic Force may assist the operator to control the orientation of the AcQBlate FORCE regarding the tissue. For instance, a perpendicular orientation of the

ablation electrode would be indicated by a minimal lateral force component. In addition, the FTI parameter informs the operator about the stability of the catheter tip on the tissue, which contributes to the effectiveness of lesion creation.

The tip design of the AcQBlate FORCE allows the application of a heparinized saline flow to be dispensed through the irrigation holes of the tip. Irrigated RF ablation is intended to allow the application of a relatively high RF power without overheating the tissue surface. This may increase the effectiveness of lesion creation.

As part of the manufacturing process, each AcQBlate FORCE is individually calibrated in order to associate the optical signal with the actual contact force. This calibration data and additional manufacturing data are stored in an RFID chip integrated in the fiber optics connector of the AcQBlate FORCE. Upon connection of the AcQBlate FORCE with the Qubic Force, these data are automatically read by the Qubic Force and used to provide catheter-specific, calibrated contact force information. As a result, a separate calibration procedure before using the catheter is not required, and the contact force reading is accurate after zero-setting the contact force while the AcQBlate FORCE is free-floating in the heart chamber (i.e., no contact with the cardiac wall).

5.7 Investigational Devices

Table 5describes the investigation devices and cables that will be used as part of the AcQForce Flutter study.

Table 5. Investigational Devices and Cables with Product Numbers

Product(s)	Model(s)
AcQBlate FORCE (Acutus)	900202, 900203, 900204, 900205, 900206
Qubic Force (Acutus)	900012
Qiona Irrigation Pump (Biotronik)	406935
Qiona Irrigation Tubing Set (Biotronik)	365775
Qubic RF Generator (Biotronik)	396166
Qubic RF Foot Switch (Biotronik)	404964
Power cord US	NK-11*
Cable for recording system analog connection (analog signal cable that transmits the ECG signals of the ablation catheter to the Recording System, where all ECG signals are collected and displayed)	MPK-4-R *
Neutral electrode/grounding pad	PK-153*
Patient cable to connect Qubic Force or Qubic RF to AcQBlate FORCE	PK-147*
Cable to grounding or neutral electrode (connects the neutral electrode, a patch usually on the leg of the patient, with the generator to close the current loop between catheter-patient-generator)	PK-148*
Cable to control unit to the Qubic RF unit (ethernet cable to connect the RF generator and the remote unit's digital communication)	VK-118*
Cable for connecting the Qiona Irrigation pump to the RF unit	VK-119*
Cable for connecting the Qubic RF unit to an EP recording system digital connection	VK-120*
Video Cable for Connecting an External Monitor to Qubic Force	VK-124*
Adapter Cable for connecting AcQMap to Qubic RF	800630*

*Or sponsor specific equivalent

6 CLINICAL INVESTIGATIONAL PLAN/ PROTOCOL

6.1 Clinical Study Objective

The objective of the study is to demonstrate the AcQBlate Force Sensing System is safe and effective when used to ablate the cavotricuspid isthmus (CTI) for the treatment of typical atrial flutter when compared to a literature-based control.

Data will be used to support a PMA application.

6.2 Clinical Study Design

The AcQForce Flutter clinical study is a prospective, multi-center, non-randomized global clinical study designed to demonstrate the safety and efficacy of the AcQBlate Force Sensing Ablation System in the ablation management of symptomatic cavotricuspid isthmus dependent atrial flutter. The subject population will consist of men and women 18 years of age or older, presenting for a *de novo* percutaneous cardiac ablation of symptomatic, typical atrial flutter.

6.3 Primary Endpoints

6.3.1 Safety

The Primary Safety Endpoint for the AcQForce Flutter study is a comparative analysis of subjects who are free from a composite list of pre-specified device/procedure related Serious Adverse Events (SAEs) that occur through 7-days post ablation procedure using a literature-based control.

Serious adverse events are pre-defined and include:

- Death
- Cardiac tamponade/perforation
- Myocardial infarction
- Stroke
- Systemic embolism
- Major access site complications
- Major bleeding requiring transfusion
- Complete heart block
- Other SAEs/SADEs adjudicated by an independent review as “probably or definitely related” to the Investigational device.

All adverse clinical events will be collected, coded and reported, for the duration of the study according to the definitions of EN ISO 14155. The occurrence rate for all the clinical events will be characterized and calculated by independent adjudication. Table 6 outlines SAE definitions.

Table 6. Serious Adverse Event Definitions

SAE	Study Definition
Death	Cessation of life
Cardiac tamponade/perforation	Development of a significant pericardial effusion during or within 30-days of the procedure. A significant pericardial effusion is one that results in: • hemodynamic compromise; or • requires elective or urgent pericardiocentesis; or • results in a 1 cm or more pericardial effusion as documented by echocardiography.
Myocardial Infarction	Presence of any one of the following criteria: • detection of ECG changes indicative of new ischemia (new ST T wave changes or new left bundle branch block (LBBB)) that persist for more than 1 hour; • development of new pathological Q waves on an ECG; imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
Stroke	Rapid onset of a focal or global neurological deficit with at least one of the following: • change in level of consciousness. • hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body; • dysphasia or aphasia, hemianopia, amaurosis fugax; • other neurological signs or symptoms consistent with stroke. Duration of a focal or global neurological deficit should be > 24 hours (less if therapeutic intervention(s) were performed (e.g., thrombolytic therapy or intracranial angioplasty)). Confirmation of the diagnosis by at least one of the following: • neurology or neurosurgical specialist; • neuroimaging procedure (Magnetic resonance imaging (MRI) or computed tomography (CT) scan or cerebral angiography; • lumbar puncture (i.e., spinal fluid analysis diagnostic of intracranial hemorrhage).

Systemic embolism	Acute vascular insufficiency or occlusion of the extremities or any non-CNS organ associated with clinical, imaging, surgical/autopsy evidence of arterial occlusion in the absence of other likely mechanism (e.g. trauma, atherosclerosis, or instrumentation). When there is presence of prior peripheral artery disease, angiographic, surgical or autopsy evidence is required to show abrupt arterial occlusion.
Major access site complications	Vascular access complications include development of a hematoma, an arteriovenous (AV) fistula, or a pseudoaneurysm. A major vascular complication is defined as one that requires surgical or pharmacologic intervention.
Major bleeding requiring transfusion	Significant bleeding that requires and/or is treated with transfusion of blood products (≥ 2 units).
Complete heart block	Cardiac conduction block of the AV node requiring the implantation of a permanent pacemaker.
Other SAEs/SADEs adjudicated by an independent review as "probably or definitely related" to the Investigational device.	A complication that results in permanent injury or death, requires intervention for treatment, or prolongs or requires hospitalization for more than 48-hours.

6.3.2 Efficacy

The Primary Effectiveness Endpoint for the AcQForce Flutter study is an analysis of subjects achieving acute procedural success. Acute procedural success is defined as the demonstration of bidirectional cavotricuspid isthmus block at least twenty (20) minutes following the last radiofrequency application at the cavotricuspid isthmus with the investigational catheter.

Bidirectional block (BDB) confirmation is defined as:

- Demonstration of bidirectional electrophysiological conduction block through the cavotricuspid isthmus (CTI) using both coronary sinus ostium (CS) and annular low right atrial pacing maneuvers.

6.3.2.1 Primary Efficacy Endpoint Failure

A primary efficacy failure will comprise the following:

- The inability to achieve and maintain bidirectional CTI block at least 20 minutes following the last RF application with the investigation device. A second investigative catheter or alternate catheter curve may be used prior to designation as failure. Maximum RF time before considering a non-investigational catheter is at the discretion of the Investigator but shall not exceed 60 minutes of RF time.

OR

- The use of a commercially available non-investigational catheter for any ablation of the CTI.

NOTE: Use of isoproterenol is at the discretion of the Investigator.

6.3.2.2 Observational Effectiveness Endpoint

The observational effectiveness endpoint is an analysis of the freedom from recurrence of typical CTI dependent atrial flutter OFF Class I/III antiarrhythmic drugs (AADs) at 30-days post index procedure measured by a 24-hour continuous electrocardiogram (ECG) monitor.

6.4 Clinical Study Duration

The study is anticipated to take approximately 12-months to enroll and will include a 30-day follow-up period. Total study duration is anticipated to be 12-18-months. The per patient study duration is expected to be approximately 6-weeks.

6.4.1 Clinical Study Sample Size

The sample size consists of 110 mITT subjects, based on using a one-sided α of 0.05 and at least 90% power for the comparison of each primary endpoint against the corresponding performance goal. A maximum of 120 mITT subjects will be enrolled.

6.4.2 Clinical Study Site Enrollment

Enrollment at any single clinical center will be limited to 20% of the maximum enrollment. Clinical centers will be informed in writing by the Sponsor when they have met any of the enrollment limits.

6.5 Clinical Study Sites

TBD

6.6 Subject Population

The subject population will consist of men and women 18 years or older, presenting for a *de novo* cavotricuspid ablation for symptomatic typical atrial flutter.

6.6.1 Inclusion Criteria

A potential study subject will meet all of the following inclusion criteria:

1. Subjects are clinically indicated for de novo catheter ablation of typical atrial flutter.
2. At least one (1) documented episode of typical flutter within 180-days (6 months) prior to enrollment, documented by 12-lead ECG.
3. Age 18 years or older at time of consent.

4. Subjects are willing and able to provide written informed consent to participate in the study and agree to comply with all follow-up visits and evaluations.

6.6.2 Exclusion Criteria

A potential study subject who meets any of the following criteria will be excluded from participation:

1. In the opinion of the Investigator, any contraindication to the planned atrial ablation, including contraindications to anticoagulation therapy and any other significant uncontrolled or unstable medical condition (e.g. sepsis, acute metabolic illness, chronic kidney disease).
2. Inability to document cavotricuspid isthmus conduction.
3. Any prior right atrial cavotricuspid isthmus ablation.
4. Any cardiac ablation for non-atrial flutter arrhythmias within 90 days prior to enrollment.
5. Any patient scheduled or anticipating an AF ablation within the follow-up period.
6. Administration of oral amiodarone within 120 days prior to procedure excluding a one-time IV/oral administration of < 2000 mg in a 24-hour period.
7. Cardiac surgery within 60 days prior to enrollment.
8. ST-elevation myocardial infarction (STEMI) within 60-days prior to enrollment.
9. Current unstable angina.
10. Documented atrial or ventricular tumors, clots, thrombus, within 30-days prior to enrollment.
11. Any history of a known hematologic disorder (bleeding/clotting).
12. Implantation of permanent leads of an implantable device in or through the right atrium within 90-days prior to enrollment.
13. Subjects with New York Heart Association (NYHA) Class IV heart failure within 6-months prior to enrollment.
14. Subjects with an ejection fraction less than 30% within 90-days of enrollment.
15. Percutaneous Transluminal Coronary Angioplasty (PTCA) within 30-days of enrollment.
16. Clinically significant moderate to severe structural heart disease (including tricuspid valve regurgitation, tricuspid valve stenosis, tricuspid valve replacement, Ebstein's anomaly, or other congenital heart disease) that would preclude catheter introduction and placement, as determined by the Investigator.
17. Any cerebral ischemic/infarct event (excluding transient ischemic attacks) within 180 days prior to enrollment.
18. Body Mass Index (BMI) >42 kg/m^2.

19. International Normalized Ratio (INR) > 3 (required for patients taking warfarin).
20. Severe uncontrolled systemic hypertension (systolic pressure > 240 mm Hg) within the last 30-days.
21. Women who are pregnant or plan to become pregnant within the course of their participation in the investigation.
22. Current enrollment in any other study protocol where testing or results from the study may interfere with the procedure or outcome measurements for this study.
23. Any other condition that, in the judgment of the Investigator, makes the patient a poor candidate for this procedure, the study or compliance with the protocol (includes vulnerable patient population, mental illness, addictive disease, terminal illness with a life expectancy of less than two years, extensive travel away from the research center).

6.7 Clinical Study Enrollment Definitions

For the purposes of this clinical study, the following definitions regarding the status of a subject will apply:

Enrolled Subject – Any subject who has signed an informed consent form, is deemed study eligible by meeting all of the inclusion and none of the exclusion criteria up to the point of the procedure.

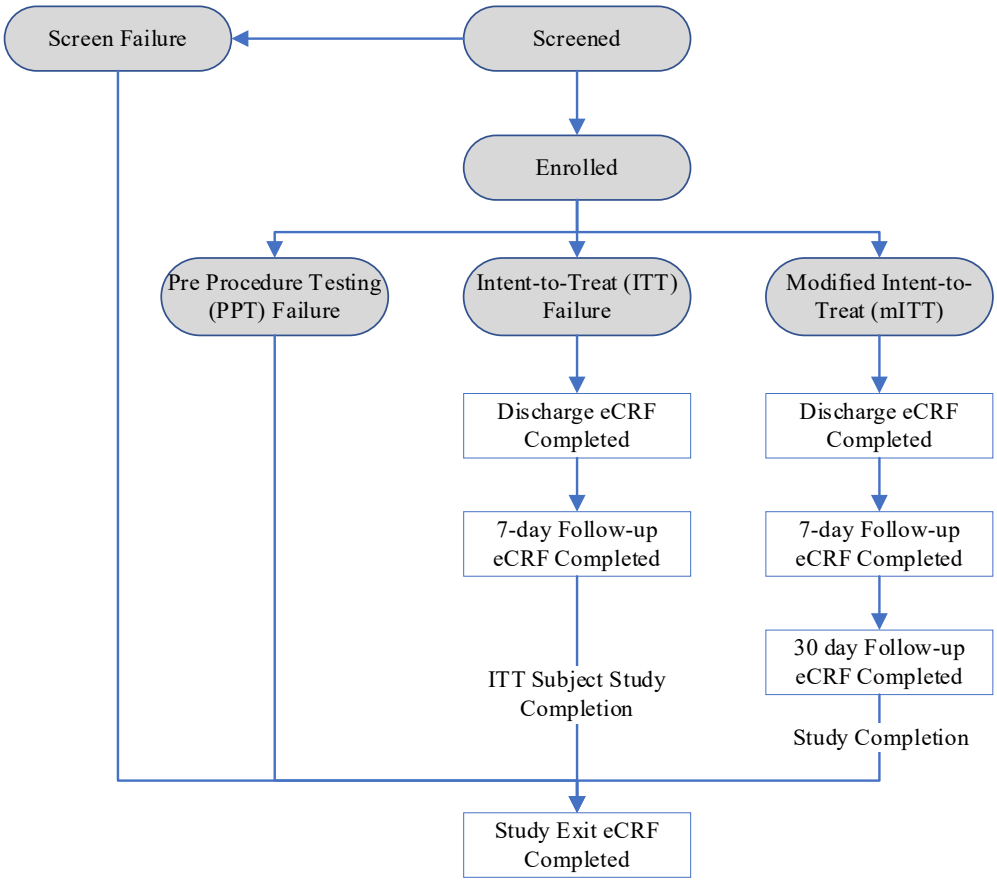
Pre-procedure Testing Failure (PPT) – An enrolled subject who has presented for the procedure in any rhythm other than sinus rhythm or typical atrial flutter and has not undergone venous access. These subjects will be treated per the recommendations of the study physician and exited from the study. No use of the investigational device is allowed. A Study Exit electronic case report form (eCRF) will be completed.

Intent-to-Treat Failure Subject (ITT) – Any enrolled subject who has the venous access portion of the ablation procedure initiated and up to the point of completion of the right-atrial access but prior to any RF application with the investigational device. The ITT population will be followed for safety reasons through the 7-day follow-up visit. ITT subjects that the AcQBlate FORCE Catheter has been inserted into will be included in the safety data analysis but excluded from the efficacy data analysis. All other ITT patients will be excluded from any safety or efficacy data analysis. In addition to the Discharge eCRF and the 7-day Follow-up eCRF, a Study Exit eCRF will also be completed. The ITT population may include:

- At the time of the procedure, if the subject does not demonstrate conduction through cavotricuspid isthmus, the subject will be exited from the study and followed for safety through the 7-day follow-up visit.

- At the time of procedure, if atrial fibrillation is initiated during the process of inducing typical AFL, a direct current cardioversion (DCCV) may be performed to attempt conversion to sinus rhythm so that the CTI conduction portion of the study may proceed. If during confirmation of CTI conduction, the investigator determines that further ablation beyond the CTI is warranted the subject will be exited from the study and followed for safety through the 7-day follow-up visit.

Modified Intent-to-Treat Subject (mITT) – Any enrolled subject who initiates the ablation procedure using the AcQBlate Force Sensing System. An initiated ablation procedure is defined as a procedure where the AcQBlate Force Sensing System is used for the ablation procedure irrespective if a non-investigational device was used to complete the ablations. mITT subjects will be followed for all study outcome measures for the full duration of the clinical study and will comprise the data set for the Primary Safety and Efficacy Endpoints.



Clinical Study Enrollment Definitions Flow Chart

6.8 Minimization of Bias

Subject selection, subject treatment, and the evaluation of study data are sources of bias. Efforts to minimize potential bias include, but are not limited to:

- Prior to enrollment, rigorous screening will be performed to confirm enrollment eligibility with defined inclusion and exclusion criteria.
- Baseline characteristics and medical history will be collected to statistically access possible characteristics that may influence study endpoints.
- All clinical study site personnel and sponsor/delegate personnel will be thoroughly trained on their respective aspects of the clinical study.
- All Investigators will be trained on and required to follow the Clinical Investigational Plan (CIP)/protocol.
- Monitoring visits will be undertaken to verify eCRFs against source data and compliance with the CIP/protocol.
- An independent clinical events adjudication reviewer will regularly review and adjudicate adverse events and deaths.
- A centralized evaluator will be used to describe atrial arrhythmia data received from the continuous ECG monitor.

6.9 Subject Withdrawal

Individual subjects may withdraw their consent to participate in the study at any time. An Investigator may discontinue a subject's participation in the study at any time to protect the safety, rights, or welfare of the subject.

Subjects missing follow-up visits will not be considered lost to follow-up (LFU) until adequate attempts to contact the subject have been made. The Investigator or designee will attempt to contact a subject at least 3 times prior to designating them as lost to follow-up; 1 of these 3 attempts should include contacting the subject via certified mail. A Study Exit eCRF form will be completed when a subject is lost to follow-up.

7 CLINICAL STUDY TREATMENTS AND FOLLOW-UP VISITS

7.1 General Overview

The clinical study is a single-arm evaluation of subjects diagnosed with cavotricuspid isthmus dependent typical atrial flutter. All subjects will undergo ablation of the cavotricuspid isthmus (CTI) for the treatment of typical atrial flutter.

7.2 Informed Consent

It is the responsibility of the Investigator (or designee) to give each subject full and adequate verbal and written information regarding all aspects of the study procedure, device, and associated risks. A signed ICF must be obtained from the subject before any study procedures not considered standard of care (SOC) for an AFL ablation are undertaken. The informed consent form (ICF) must be signed by the subject and witnessed by the Investigator (or designee). The original signed ICF is filed in the subject's study records with one copy placed in the subject's medical notes and one copy provided to the subject.

7.3 Subject Screening

The following information should be collected to verify eligibility in the clinical study:

- Review of all inclusion/exclusion criteria to confirm subject eligibility
- Subject demographics
- Medical history review including:
  - Information specific to the exclusion criteria
  - History of atrial fibrillation
- Physical examination (at a minimum Cardiovascular, Respiratory, Extremities should be evaluated)
- Vital signs
- 12-lead ECG documenting episode of cavotricuspid dependent typical atrial flutter within 180 days (6-months) of enrollment
- Subject symptoms
- Current cardiovascular and anticoagulation medications

7.4 Baseline Evaluation

The following information should be collected at baseline and reviewed prior to the ablation procedure:

- TTE within 90 days of procedure (if needed)
- 12-lead ECG
- Pregnancy test for women of childbearing potential within 7-days prior to the study procedure following the institution's SOC

7.5 Ablation Pre-Procedure Requirements

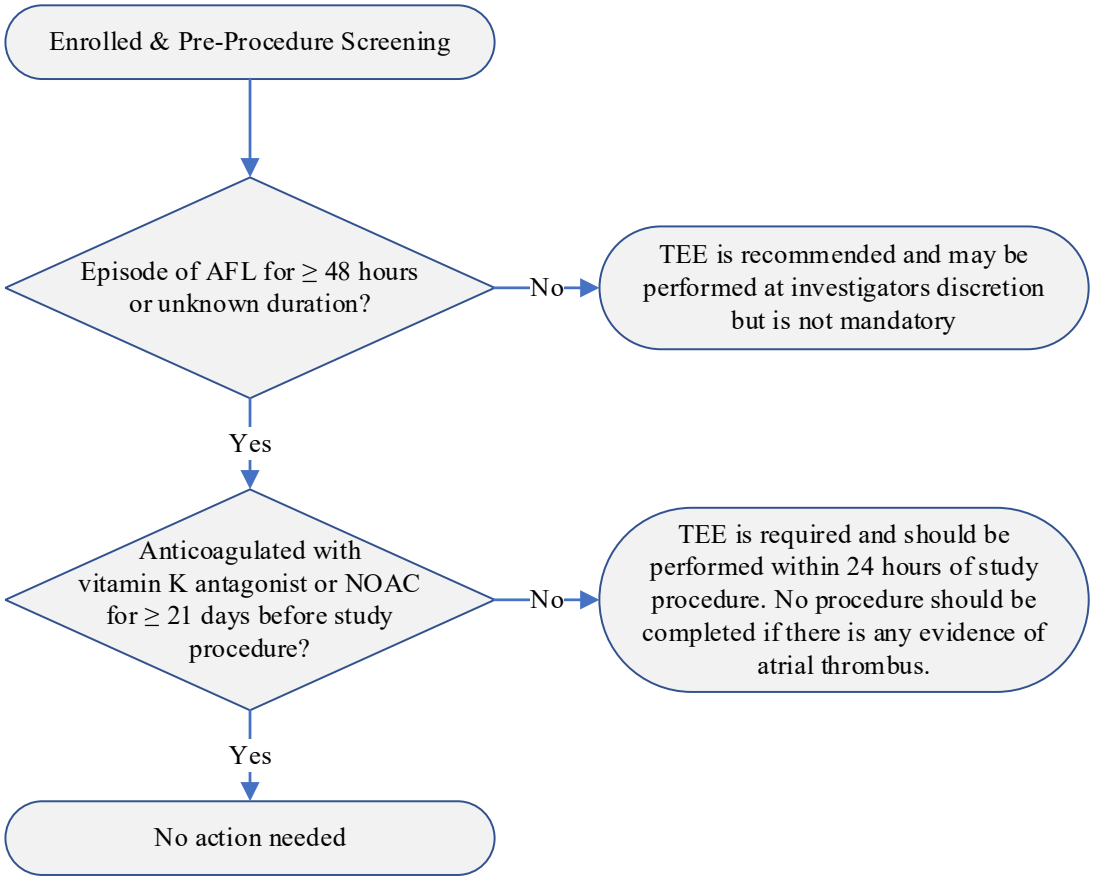
7.5.1 Atrial Thrombus

No procedure should be completed if there is any evidence of atrial thrombus. The method of thrombus assessment should be recorded on the Procedure eCRF.

7.5.2 Anticoagulation and Atrial Thrombus Assessment

Periprocedural anticoagulation and pre-procedure assessment for atrial thrombus should follow the 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation and the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation

- A transesophageal echocardiogram is required for all subjects with atrial flutter for ≥ 48 hours or unknown duration AND the subject has not been anticoagulated with a vitamin K antagonist or NOAC for at least 21 days before the study procedure.
    - A transesophageal echocardiogram for subjects with atrial flutter less than 48 hours duration prior to study procedure may be performed at the investigators discretion but is not mandatory.
- Subjects who are required to have a transesophageal echocardiogram, should have one performed within 24 hours of the study procedure.
- Any subject who is determined to have cardiac thrombus will not undergo the study procedure and will be exited from the study.



Transesophageal Echocardiogram Requirement Flow Chart

7.5.3 Antiarrhythmic Medications

To minimize the impact of oral antiarrhythmic drugs (AADs), on device effectiveness, Class I/III AADs should be discontinued at least 5 half-lives (Table 7) prior to the ablation procedure.

Table 7. Antiarrhythmic Medication 5 half-lives

Antiarrhythmic Medication	5 Half-lives
Class I	
Lidocaine	7.5-10 hours
Procainamide	15-20 hours
Propafenone	15 hours- 2 days
Class III	
Amiodarone*	120 days

Dronedarone	5 days
Sotalol	2-4 days
Ibutilide	12 hours-2.5 days

*Exclusion Criteria #6: Administration of oral amiodarone within 120 days prior to procedure excluding a one-time IV/oral administration of ≤ 2000 mg in a 24-hour period.

7.5.4 Subject Preparation

Subjects will be prepped and draped for the ablation procedure following standard hospital practice. This includes placement of all cables/patches used for ECG monitoring and operation of all devices to be used during the procedure.

7.5.5 Anesthesia

Use of conscious sedation or general anesthesia will follow the Investigator preferences as directed by the subject's health status.

7.5.6 AcQBlate Force System Set-Up

The AcQBlate Force System including the AcQBlate FORCE catheter, the Qubic RF Generator, the Qiona Irrigation Pump, Tubing Set, and assorted cables should be prepared and connected following the IFU and Investigator training. During the procedure, Acutus Medical personnel will be available to provide onsite training on any aspects of the AcQBlate Force System set-up and operation.

7.6 CTI Ablation Procedure

7.6.1 Confirmation of Conduction through the CTI

Entrainment pacing from the cavotricuspid isthmus during atrial flutter will be attempted prior to initiating RF ablation to verify that the CTI is part of the arrhythmia circuit. When clinically reasonable, the investigator may attempt to induce atrial flutter using pacing maneuvers when the subject presents to the lab in sinus rhythm.

Documentation of concealed entrainment should be printed and recorded on the appropriate eCRF.

If Investigator is unable to induce and entrain CTI dependent AFL, the Investigator may choose to confirm and document conduction through the CTI. CTI conduction must be confirmed prior to initiating RF ablation. Documentation of inability to induce and/or entrain should be printed and recorded on the appropriate eCRF. Confirmation of conduction through the CTI should be demonstrated using pacing maneuvers.

Documentation of conduction through the CTI should be printed and recorded on appropriate CRF.

If CTI dependent AFL cannot be confirmed or CTI conduction cannot be confirmed, the subject will be considered an ITT failure subject and exited from the study at the 7-day follow-up visit.

If during inducement, entrainment, or other pacing maneuvers the subject is paced into AF, DCCV may be performed to attempt conversion to sinus rhythm so the CTI conduction measurement may proceed. If the investigator determines further ablation beyond the CTI is warranted the subject will be exited from the study after being followed for 7-days for safety.

The AcQBlate FORCE catheter shall not be used to initiate ablation procedure until conduction through the CTI is confirmed.

7.6.2 Ablation Considerations

In order to reduce the risk of complications the following measures need to be considered for ablation of the atria. Recommended ablation target values are identified in Table 8 below.

- Titrate the energy, starting with an initial power of ≤ 25 W. Do not exceed 30 W.
- If a transmural lesion is not achieved, defined by 70% - 80% reduction of the intracardiac electrogram (IEGM) signal or emergence of double potentials of equal and low amplitude, after 20 seconds the energy may be increased but not in excess of 40 W. Ablations at 31-40 W should not exceed 15 seconds in duration.
- Avoid excessive ablation durations at any focal location. If focal ablations are applied, duration of RF power at one location requires careful attention to commonly used ablation effectiveness parameters such as electrogram amplitude reduction, electrogram morphology change or impedance changes.
- Avoid excessive contact force while using a steerable sheath to guide the ablation catheter.
- Optimal contact force is 3-20 g. Do not exceed 40 g for prolonged periods.
- Do not increase power only because no or little temperature increase is measured by the AcQBlate FORCE and the Biotronik Qubic RF ablation generator. The tip of the AcQBlate FORCE has good cooling properties to avoid thrombus formation. The displayed temperature reflects the temperature of the irrigated electrode, not of the tissue.
- Irrigation flow rate must follow the IFU.
- Use of half-normal saline is not allowed.

Table 8. Recommended Target Values for Ablation

Parameter	Value	Value
Power Range*	10 to 30 Watts	31 to 40 Watts
Irrigation flow rate during RF application	8 ml/min	15 ml/min
RF Ablation Energy Delivery**	< 60 seconds	< 15 seconds
Temperature monitoring during RF application***	40° - 50° C	
Contact Force Range	3 grams to 20 grams	

* It is recommended that lower power levels be used and titrated up to 40W when clinically effective ablation cannot be achieved at lower energy levels and within the contact force range. Maximum power must not exceed 40W. Note that high power levels increase the risk of steam pops, perforation, char, coagulum and/or extracardiac damage, especially when applied to the posterior wall. Impedance drops, electrogram reduction and/or electrogram morphology change may be used to guide RF termination.

** Maximum duration of ablation applies to the duration of RF ablation energy delivery at the same location. Duration of ablation as well as the decision to interrupt RF power delivery at any time during RF ablation should be guided by the clinical judgement of the investigator and monitoring of commonly used ablation effectiveness parameters such as electrogram amplitude reduction, electrogram morphology change or impedance changes.

*** The temperature displayed on the RF generator is not representative of the tissue temperature or the temperature of the electrode-tissue interface.

Warning: Higher contact forces may not improve the characteristics of lesion formation and may increase the risk for perforation during manipulation of the catheter.

7.6.3 CTI Ablation

Ablation of the CTI using the investigational device should follow the Investigator's standard of care. Use of a deflectable long vascular sheath to achieve catheter stability is encouraged. Pacing from the CS during the ablation is at the discretion of the Investigator. Power and irrigation flow setting should follow Table 8. Ablation beyond the CTI is not allowed. No left sided ablations are allowed.

7.6.4 Confirmation of Bidirectional Block

Initial bidirectional block (BDB) confirmation should meet the study endpoint definition of:

- Demonstration of bidirectional electrophysiological conduction block through the cavotricuspid isthmus (CTI) using both coronary sinus ostium (CS) and annular low right atrial pacing maneuvers.

This acute endpoint should be re-confirmed at least 20-minutes following the last RF ablation with the investigational device. If recovery of isthmus conduction occurs, additional ablations should be performed at the site of the reconnection, and the confirmation/reconfirmation steps must be repeated. A reset of the 20-minute wait time for reconfirmation is required. A second investigative catheter or alternate catheter curve may be used prior to designation as ablation failure. Maximum RF time before considering a non-investigational catheter is at the discretion of the Investigator but shall not exceed 60 minutes of RF time. If the Investigator is unable to achieve bidirectional block with the investigational catheter(s), it is recommended, at the Investigator's discretion, to use a commercially available ablation catheter approved for typical atrial flutter to complete the procedure.

7.7 Post Ablation Recovery

At the conclusion of the procedure, the subject should be recovered following the Institution's standard practice. Sheath removal may be completed when acceptable hemostasis can be achieved. The use of protamine to reverse anticoagulation is at the discretion of the Investigator. Protamine use will be recorded on the Procedure eCRF.

7.8 Procedure Data Collection

Collection of data generated as a result of the procedure should include:

- Print out of 12-lead ECG at procedure start
- Print out of intracardiac AFL
- Print out of entrainment pacing results pre-ablation for the CTI
- Print out of attempts to prove conduction through the CTI
- Print out of 12-lead ECG at end of procedure
- Demonstration of initial BDB
- Demonstration of BDB 20 minutes following initial determination
- Total procedure time (from first venous access to last cardiac catheter removed)
- Total ablation time for CTI ablation
- Total fluoroscopy time for the CTI ablation procedure
- Cumulative irrigation volume for CTI ablation
- Pre-set parameters for RF power and temperature
- Maximal parameters for RF power and temperature for CTI ablation
- Number of RF applications for CTI ablation

- Cross over of any non-investigational catheter (including reason for change out)
- Recording of all IV cardiac medications and anticoagulation infused during the procedure
- Usability characteristic data will be collected.
- Device identification

7.8.1 Post Ablation Recovery

Post ablation recovery and removal of the introducer sheaths should follow the institution's standard of care.

7.8.2 Post Ablation Antiarrhythmic Use

Following the ablation procedure, Investigators are encouraged to discontinue all Class I/III AADs. If continuation of an AAD is clinically indicated, it must be discontinued at least 5 half-lives (Table 10) prior to the 30-day arrhythmia assessment. Changes in any AAD medication will be recorded on the concomitant medication eCRF.

7.8.3 Post Ablation Anticoagulation Use

Due to the potential of atrial stunning following conversion from AFL to SR and to prevent the risk of thromboembolic events, it is recommended that therapeutic anticoagulation be given for at least four (4) weeks with all subjects that presented with pre-ablation AFL of ≥ 48-hours. All anticoagulation medications will be recorded on the concomitant medication eCRF.

7.8.4 Hospital Discharge

The following evaluations must be completed prior to discharge (see Table 12):

- Arrhythmia History since the procedure
- Physical Exam (at a minimum Cardiovascular, Respiratory, Extremities should be evaluated)
- Vital Signs
- Symptoms
- Medications
- Adverse Events
- 12-lead ECG
  Note: in the event that post-procedure 12-lead ECG documented sinus rhythm

AND post-procedure 12-lead ECG was taken ≤ 6 hours from discharge, the post-procedure 12-lead ECG may be used to satisfy this requirement.

Careful attention should be placed in the identification of potential cardiac effusions and post-procedure cardiac tamponade. Unexplained reduction in blood pressure, chest pain or shortness of breath may require a post-procedure Transthoracic Echo (TTE) and further evaluation and management as indicated.

7.9 Follow-up Visits

Screening, procedure, and follow-up visits are outlined in Table 9.

All treatment subjects will have data collected at screening, procedure, hospital discharge, 7- and 30-days post procedure. The table below outlines the procedures and testing performed while enrolled in the clinical study.

Table 9. Schedule of Events

Study Activities	Screening & Baseline	Ablation Procedure	Pre-Discharge	7-Days (± 3-days Phone call)	30-Days (± 7-days)	Unscheduled Follow-up*
Informed Consent	**X**					
Medical History & Physical Exam	**X**		**X**		**X**	**X**
Medications	**X**	**X**	**X**	**X**	**X**	**X**
Transthoracic Echo (TTE) (if needed)	**X** Within 90 days of index procedure					
Thrombus Assessment: Transesophageal Echocardiogram (TEE) **		**X**				
Adverse Events		**X**	**X**	**X**	**X**	**X**
Symptom History	**X**		**X**	**X**	**X**	**X**
12-lead ECG	**X**	**X**	**X**		**X**	**X**
24-hour Holter or patch monitor					**X**	**X**
SOC Pre-procedure Labs	**X**					
Pregnancy Test (female subjects of childbearing age)	**X**					

*Only required if subject reports symptoms associated with cardiac arrhythmia or in the case of a procedure related adverse event

**A transesophageal echocardiogram is required for all subjects with atrial flutter for ≥ 48 hours or unknown duration AND the subject has not been anticoagulated with a vitamin K antagonist or NOAC for at least 21 days before the study procedure. Subjects who are required to have a transesophageal echocardiogram, should have one performed within 24 hours of the study procedure (reference section 7.5.2)

7.9.1 7-Day Follow-up Visit

Subjects will be contacted by phone by the clinical study team at 7-days (7 ± 3-days) following their discharge from the hospital. Information regarding their groin access site(s) and sense of any irregular heart rate must be obtained. If, during the phone discussion any concerns arise that suggest AEs, at the Investigator's discretion, the subject may be asked to return to clinic for a thorough evaluation.

The following evaluations will be performed during the telephone follow-up visit. Data will be recorded on the Follow-Up Visit eCRF.

- Medication history
- Symptoms
- Adverse events assessment

7.9.2 30-Day Follow-up Visit

Subjects will be seen in the study center clinic 30-days (30 ± 7-days) post ablation.

The following evaluations will be performed during the clinic follow-up visit. Data will be recorded on the Follow-Up Visit eCRF.

- Physical exam (at a minimum Cardiovascular, Respiratory, Extremities should be evaluated)
- Vital signs
- Medication history
- Symptoms
- Adverse events assessment
- 12-lead ECG
- 24-hour Holter or patch monitor

7.9.3 Unscheduled Visits

Any visit outside of the scheduled follow-up visit windows will be considered an unscheduled visit. All pertinent data will be recorded on the Follow-up Visit eCRF.

8 STATISTICAL METHODS

8.1 Assumptions for Statistical Analysis

The following assumptions were used in the calculation of sample size:

Endpoint	Literature Based Control	Statistical Margin	Performance Goal	Acutus Estimate	(90% Power α 0.050)
Primary Safety	97.0%	5.5%	93.0%	98.5%	110
Primary Efficacy	93.7%	10%	83.7%	93.7%	85

8.2 Statistical Methods for Safety Evaluation

The primary safety endpoint, the proportion of mITT and select ITT subjects who are free from device/procedure related SAE that occur through 7-days post ablation procedure, will be analyzed using a binomial proportion test. Subjects who do not have evidence of a SAE/SADE from the composite list of safety events will be considered a success.

8.2.1 Primary Safety Endpoint Hypothesis

The null and alternate hypotheses for primary safety endpoint are as follows:

Ho: The proportion subjects in the mITT and select ITT subjects (ρ) who are free from device/procedure related SAE through 7-days post ablation procedure is less than or equal to 93.0%.

$$\text{Ho: } \rho \leq 93.0\%$$

Ha: The proportion subjects in the mITT and select ITT subjects (ρ) who are free from device/procedure related SAE through 7-days post ablation procedure is greater than 93.0%.

$$\text{Ha: } \rho > 93.0\%$$

The null hypothesis will be rejected if the one-sided 95% Clopper-Pearson Exact lower confidence bound is greater than 93.0%.

8.2.2 Other Safety Analyses

Individual procedure-device related SAEs at 7-days will be analyzed by event frequencies and proportions of subjects. Total and individual non-serious procedure-device AEs at 30-days will also be analyzed by event frequencies and proportion of subjects. Adverse events will be analyzed in terms of their severity, action taken, and duration to resolution.

Device Deficiency Reports will be analyzed for frequencies of safety events and proportion of subjects as part of the safety analyses.

8.3 Statistical Methods for Efficacy Evaluation

The primary efficacy endpoint, the proportion mITT subjects (β) demonstrating bidirectional block (BDB) of the CTI confirmed at 20 minutes following the last right atrial radiofrequency (RF) application using the investigational catheter, will be analyzed using a binomial proportion test.

8.3.1 Primary Efficacy Endpoint Hypothesis

The null and alternate hypotheses for primary efficacy endpoint are as follows:

Ho: The proportion of mITT subjects (β) demonstrating bidirectional block (BDB) of the CTI confirmed at 20 minutes following the last right atrial radiofrequency (RF) application using the investigational catheter is less than or equal to 83.7%.

$$\text{Ho: } \beta \leq 83.7\%$$

Ha: The proportion of mITT subjects (β) demonstrating bidirectional block (BDB) of the CTI confirmed at least 20 minutes following the last right atrial radiofrequency (RF) application using the investigational catheter is greater than 83.7%.

$$\text{Ha: } \beta > 83.7\%$$

The null hypothesis will be rejected if the one-sided 95% Clopper-Pearson Exact lower confidence bound is greater than 83.7%.

8.4 Study Success Criteria

The study success criteria is defined as the rejection of the null (Ho) hypotheses for safety and efficacy as defined in sections 8.2.1 and 8.3.1, respectively.

- Safety Ho: The proportion subjects in the mITT and select ITT subjects (ρ) who are free from device/procedure related SAE through 7-days post ablation procedure is less than or equal to 93.0%.

$$\text{Ho: } \rho \leq 93.0\%$$

- Efficacy Ho: The proportion of mITT subjects (β) demonstrating bidirectional block (BDB) of the CTI confirmed at 20 minutes following the last right atrial radiofrequency (RF) application using the investigational catheter is less than or equal to 83.7%.

$$\text{Ho: } \beta \leq 83.7\%$$

8.5 Primary Endpoints Sensitivity Analysis

Acutus Medical, Inc. and participating investigators will exercise their best efforts to ensure subjects are not lost to follow-up and that there is a minimal amount of missing data. However, it is recognized that some degree of missing data may exist. To address the potential impact of any such missing data, sensitivity analyses of the primary safety and efficacy endpoints will be performed using the mITT and select ITT Cohorts.

8.6 Primary Endpoints Subgroup Analysis

Subgroup analyses of the primary safety and efficacy endpoints are exploratory. No labeling claims are planned. A Pearson chi-squared test will be performed for any significant differences between gender, ethnicity, race and individual co-morbidities and using a logistic regression test for age.

8.7 Secondary Endpoints

There are no secondary endpoints established for this study.

8.8 Study Sample Size Rationale

The sample size requirement for this protocol was determined using the Statistical Analysis System (SAS) Software (Cary, NC) Proc Power one sample proportion using a normal-approximate z test, with at least 90% power and a one-sided 5% significance level.

For the primary safety endpoint, assuming an estimated primary safety rate of 97% and a null hypothesis proportion of 93%, a minimum sample size of 110 subjects is required.

For the primary efficacy endpoint, assuming an estimated primary efficacy rate of 93.7% and a null hypothesis proportion of 83.7%, a minimum sample size of 85 subjects is required.

Therefore, the minimum required sample size for this study will be 110 subjects. A maximum of 120 mITT subjects will be enrolled.

8.9 Statistical Methods for Baseline, Screening, Procedural Experience and Hospital Discharge Data

Demographics, baseline data, including but not limited to relevant descriptors from the medical history, co-morbidities and medications, will be summarized.

Procedural data collection will also be analyzed and summarized.

Continuous variables are summarized as means, standard deviations, medians, and ranges. Categorical variables are summarized as frequencies and percentages. By-Subject listings of baseline and procedural data will be provided.

8.10 Other Statistical Considerations

Confidence intervals and statistical tests are performed at a two-sided 5% significance level unless specified otherwise. All p-values are rounded to four decimal places. Analyses of the study may be utilized for publication or medical conference presentation purposes if the integrity and objectives of the study are not compromised.

9 ADVERSE EVENTS

For the purpose of this CIP/protocol, an adverse event is any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs in subjects whether or not related to the AcQBlate Force Sensing System, and includes events related to the procedures involved in the CIP/protocol.

Any medical conditions, problems, signs, symptoms, or findings that occurs in a subject once they are considered a component of the "Intention to Treat" is considered an adverse event (AE). Any medical conditions, problems, signs, symptoms, and findings occurring prior to enrollment are to be reported as pre-existing conditions on the Medical History eCRF.

All AEs will be documented with the event term and description, start date, duration, severity, seriousness, relatedness to either the device or the procedure, action taken, and outcome, will be recorded on the Adverse Event eCRF. The Investigator has the responsibility of classifying any event as related to a component of the AcQBlate Force Sensing System, or the ablation procedure.

9.1 Serious Adverse Events/Serious Adverse Device Effect

A Serious Adverse Event/ Serious Adverse Device Effect is any event that:[1]

- led to death
- led to serious deterioration in the health of the subject, that either resulted in:
  - a life-threatening illness or injury, or
  - a permanent impairment of a body structure or a body function including chronic diseases, or
  - in-patient or prolonged hospitalization, or
  - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- led to fetal distress, fetal death, or a congenital anomaly or birth defect

Reports relating to the subject's subsequent medical course following an SAE must be submitted to the Sponsor until the event has subsided or, in the event of permanent

[1] EN ISO 14155:2011 section 3.37

impairment, until the event has stabilized, and the overall clinical outcome has been ascertained.

A planned, in-patient hospitalization, without a serious deterioration in health, is not considered to be an SAE.

Recurrence of atrial flutter is not considered an adverse event as there is a known recurrence rate associated with atrial flutter ablation. Scheduled hospitalizations to treat these arrhythmias will not be considered serious in nature. However, if a subject is hospitalized for a clinical condition resulting from the arrhythmia, an adverse event should be reported.

9.2 Adverse Device Effects (ADEs)

Adverse Device Effects (ADEs) are a subset of AEs. The ADEs are only those AEs caused by, or related to the device, including any AE resulting from insufficiencies or inadequacies in the instructions for use, the system components, or any product malfunction, including any event that is a result of a user error or intentional misuse.

With any procedure or treatment, there are known possible risks and complications. A list of known or anticipated ADEs is found in the CIP/protocol, IFU, and Operator's Manual (OM).

9.3 Unanticipated Adverse Device Effects (UADEs)

An Unanticipated Adverse Device Effect is any event that occurs as a result of the device use that was not identified as a known or an anticipated risk for the AcQBlate Force Sensing System, as found in the CIP/protocol, IFU, and OM for the device.

When an Investigator suspects an event meets the definition for a UADE, the event term and description, start date, duration, severity , seriousness, relatedness to either the device or the procedure, action taken, and outcome, will be recorded on the Adverse Event eCRF. Additionally, reports must be provided to the reviewing Institutional Review Board/Ethics Committee/Competent Authority (IRB/EC/CA) per national and local requirements.

The Sponsor/manufacturer must then conduct an evaluation of the suspected UADE and report the results of the findings to all reviewing IRBs/ECs/CA and participating Investigators within five (5) business days after first receiving notice of the effect.

9.4 Adverse Event Reporting

The Investigator is responsible for reporting all procedure and device related AEs that occur during the follow-up period. Initial reporting will be with the Adverse Event eCRF; however, additional information may be required by the Sponsor or any regulatory authority. The Investigator must report any SAEs, SADEs, UADEs, or Device Deficiency (DD) to the Sponsor as soon as possible after becoming aware of the event, but no later than ten (10) business days after receiving knowledge of the event occurrence. All SAEs, SADEs, and UADEs will be documented on the Adverse Event eCRF along with an explanation of any

medical treatment administered. Documentation should include the time of onset, complete description of the event, severity, duration, actions taken, and outcome.

9.5 Event Relationship to the Device

The Investigator should provide information regarding the relationship of the event to the procedure and/or the AcQBlate Force Sensing System. The device relationships and severity definitions are defined in Tables 10 and 11 below:

Table 10. Adverse Event Relationship Definitions

Not Related	The cause of the AE is known and is not related to any aspect of the AcQBlate Force System during the ablation procedure.
Possibly Related	There is a reasonable possibility that the event may be related to the ablation procedure. The AE has a **timely relationship** to the study procedure(s); **however, it follows no known pattern of response** and an alternative cause seems more likely or there is significant uncertainty.
Probably Related	It is probable that the event is related to the ablation procedure. The AE has a **timely relationship** to the study procedure(s) and **follows a known pattern of response**, but a potential alternative cause may be present.
Definitely Related	The event is definitely related to the ablation procedure. A related event has a strong temporal relationship and an alternative cause is unlikely.

Table 11. Adverse Event Severity Definitions

Mild	Event results in mild or transient discomfort, not requiring intervention or treatment; does not limit or interfere with daily activities (e.g., insomnia, mild headache).
Moderate	Event is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment (e.g., fever requiring antipyretic medication).
Severe	Event results in significant symptoms that prevents normal daily activities; may require hospitalization or invasive intervention (e.g., anemia resulting in blood transfusion).

9.6 Death Notice

When a site becomes aware of a subject's death, it will be reported to the Sponsor. Notification should be made to the reviewing IRB/EC/CA/local requirements within two (2) days of notification. The FDA will be notified within 10 days.

The materials to be submitted to the Sponsor for a death include the following:

- Death narrative including a short description by the treating physician of record at the time of death regarding the circumstances of death.
- An assessment by the Investigator as to whether the death is related to study interventions.
- A copy of the subject's death certificate if available.
- When applicable, a copy of an autopsy report.

For reported deaths, the Investigator or designee should supply the Sponsor and the presiding IRB/EC/CA with any additional requested information, if available (i.e., hospital records).

9.7 Device Complaint and Malfunction

Each clinical procedure will be attended by Acutus Medical personnel responsible for the proper use of the technology. If a malfunction occurs, the Sponsor representative will report the findings to the Clinical and Product Complaints departments. Evaluations of all complaints will follow Acutus Medical Quality Assurance Procedures (QAPs) for complaint handling.

9.8 Adverse Event Analysis

All procedure and device related AEs will be independently adjudicated. Analysis of data will follow the Safety Management Plan and the Statistical Analysis Plan. Reporting to the convening IRB/EC will follow regulatory requirements.

9.9 Clinical Events Adjudication

Acutus Medical, Inc. (or designee) will coordinate meetings with the clinical events adjudication reviewer in accordance with Acutus Medical, Inc. QAP and the Safety Management Plan for AcQForce Flutter. The selection of a qualified individual will allow for the evaluation of individual safety events for adjudication and comment on the overall conduct of the clinical trial. The qualified individual will assume the following roles:

- To review and independently adjudicate safety data by providing a standard, methodical, independent, and unbiased assessment of safety events and relationship to the clinical trial.
- To adjudicate individual adverse events within the clinical trial to determine if those events are related to the clinical trial or the investigational device.
- To periodically review and evaluate the accumulated safety data to assure the safety of subjects is protected while the scientific goals of the clinical trial are being met.

- To monitor safety data trends, reviewing issues critical to the conduct of the clinical trial as data is generated.

10 RISK: BENEFIT ANALYSIS

10.1 Risks of Clinical Study Procedures

This clinical study has been designed to involve as little pain, discomfort, fear, and any other foreseeable risk as possible for the enrolled subjects. Even when the AcQBlate Force Sensing System is used correctly, complications during and after the ablation treatment may occur.

The following AEs are associated with electrophysiology right atrial ablation procedures:

- Air embolism
- Acute Respiratory Distress Syndrome (ARDS)
- Allergic reaction/anaphylaxis
- Anemia
- Anesthesia reaction
- Arrhythmias
- AV fistula
- Cardiac tamponade/perforation
- Cardiac thromboembolism
- Chest pain/discomfort
- Complete heart block
- Congestive heart failure
- Coronary artery spasm
- Death
- Diaphragmatic paralysis
- Elevated Cardiac Enzymes
- Endocarditis
- Esophageal abrasion/erosion/perforation
- Femoral nerve injury
- Fever
- Groin hematoma/ecchymosis
- Hemothorax
- Hypotension
- Hypothermia
- Infections/sepsis
- Major bleeding requiring surgery or transfusion
- Myocardial infarction
- Obstruction, perforation or damage to the vascular system
- Oral pharyngeal injury
- Pericardial effusion
- Pericarditis
- Phrenic nerve damage
- Pleural effusion
- Pneumonia
- Pneumothorax
- Pseudoaneurysm
- Pulmonary edema
- Pulmonary embolism
- Pulmonary hypertension
- Radiation injury
- Respiratory depression
- Retroperitoneal bleeding
- Skin burns
- Stroke
- ST segment elevation
- Systemic embolism
- Thromboembolism
- Tracheal injury
- Transient ischemic attack
- Valvular damage/insufficiency
- Vasovagal reactions
- Vagal nerve injury /gastroparesis

The following ADEs may be experienced if the IFU is not followed:

- Injury to user during defibrillation.
- Excessive force, if applied, may damage the AcQBlate FORCE catheter sensor at the distal section.
- The AcQBlate FORCE may be damaged through introducer sheath if the transseptal sheath lumen is less than 8.5F.

10.2 Mitigation of Risks

The completed risk analysis (RSK-21) of the AcQBlate Force Sensing System identified all known risks to the Investigator and subject. The risks associated with a standard ablation procedure are listed in section 10.1. AcQBlate FORCE is similar in design to existing commercially available ablation catheters. AcQBlate Force Sensing System does not create new safety risks or increase procedural risks beyond those associated with commercially available ablation systems.

Pre-clinical research, and a first-in-man clinical study of the AcQBlate Force Sensing System has demonstrated that the system and catheters are safe for human use. All potential risks have been evaluated and mitigation strategies have been implemented to reduce potential risks to acceptable levels. Any additional information that would alter the risk potential will be communicated by the Sponsor.

Risks associated with participation in this clinical study are minimized through strict adherence to the inclusion and exclusion criteria outlined in sections 6.6.1 and 6.6.2, training of Investigators and staff, and CIP/protocol compliance. Subjects should be followed as described in the CIP/protocol to avoid any potential interaction with concomitant medical treatments. Acutus Medical believes that the potential benefits of the AcQBlate Force Sensing System outweigh the potential risks in the appropriate patient population and when the procedure is completed by an appropriately trained Investigator.

11 DATA QUALITY ASSURANCE

Acutus Medical will oversee the data collection for this study in accordance with the Code of Federal Regulations (CFR), Good Clinical Practices (GCP), regulatory requirements, the Data Management Plan (DMP), and corporate QAPs. Data will be collected and stored in an Electronic Data Capture (EDC) system. Data will be reviewed for accuracy and completeness by Acutus Medical (or designees). In the even any discrepancies are identified, they will be resolved with the Investigator or designees, as appropriate. In order to preserve data integrity and security of the data, access to the study in the EDC will be controlled by Acutus Medical and shall be limited to appropriately trained personnel with assigned log-on credentials.

11.1 Site Data Management

For the duration of the study, the Investigator and their designees will maintain complete and accurate documentation, including but not limited to medical records, study progress notes, laboratory reports, signed patient ICFs, correspondence with the reviewing IRB/EC/CA, correspondence with Acutus Medical (or designees) and study monitors, AE reports, and information regarding subject discontinuation/withdrawal or completion of the study.

The Investigator/Institution will permit direct access to source data and documents in order to complete study-related monitoring, audits, IRB/EC reviews, event adjudication, and regulatory inspections that may be performed. The Investigator will obtain, as part of the ICF process, permission for authorized Sponsor employees, study monitors or regulatory authorities to review, in confidence, any records that identify subjects in this study.

11.2 Data Management

The following procedures/processes will be defined in the Data Management Plan (DMP):

- procedures used for development, validation and testing of electronic clinical data systems,
- procedures used for database access and training,
- procedures used for data review, and issuing and resolving data queries,
- procedures for data lock, transfer and retention.

11.3 Subject Identification

Subjects will be identified on all eCRFs and source documents by a unique, anonymized identification reference number, which will be issued once the ICF has been signed, and the subject is added to the EDC.

11.4 Screen Failure Subjects

Subjects who are screened for the study but are not enrolled for any reason will not be followed and their data will not be used for any outcome analysis. A Study Exit eCRF will be completed. Screening and baseline data will be collected in the EDC and may be used for subset data analysis.

11.5 Subject Study Completion and Withdrawal

Subject participation will be considered concluded when the 1-month visit is completed, and all data collection is complete. Subjects who withdraw for any reason will have all available data entered into the EDC. Reasons for withdrawal will be entered on the Study Exit eCRF.

11.6 Subjects Lost-to-Follow-Up

A subject will be considered LFU from the last missed clinical evaluation if all reasonable efforts made to contact the subject and request their continued participation in the study have failed. All attempts to contact the subject will be documented. See section 6.9 for details.

11.7 Confidentiality of Data

Information regarding study subjects will be kept confidential and managed according to the requirements and regulations of the local and national governing bodies and QAPs of Acutus Medical or participating Clinical Research Organizations (CROs), and, where applicable, in compliance with the General Data Protection Regulation (GDPR).

All data and information collected during this study will be considered confidential by Acutus Medical and their delegates. All data used in the analysis and summary of this study will be anonymous and without reference to specific subject names. Access to subject files will be limited to authorized personnel of Acutus Medical (including any core labs), the Investigator, clinical site research staff, Clinical Monitors (also known as Clinical Research Associates (CRAs)) and authorized Regulatory Authorities. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study.

11.8 Source Documents

Source data encompasses all information, original records of clinical findings, observations, or other activities, which are required in a clinical study for the reconstruction and evaluation of the study. Examples of these original documents, and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subject diaries or evaluation checklists, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, copies of clinic and procedural site coding and billing records, microfiches, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at the pharmacy, and at the laboratories involved in the clinical study.

Regulations require that the Investigator maintain information in the patient's medical records that corroborate data collected for the study. To comply with these regulatory requirements, the following is a list of information that should be maintained, at a minimum:

- Medical history/general physical condition of the subject before involvement in the study, which will be of a sufficient nature to verify the CIP/protocol eligibility criteria.
- Study/progress notes, including the date of entry into the study, documenting the following:
  - The general health of the subject.
  - The discussion of the study risks and benefits with the patient.

  - Completion of the ICF process.
  - A statement that the subject reviewed and signed the patient informed consent form.
- Dated notes from each subject visit to support all data recorded on the eCRFs.
- AEs reported and their continuation or resolution at each visit, including supporting documentation, such as discharge summaries, lab results, non-invasive testing reports, etc.
- Notes regarding Antiarrhythmic Drugs (AADs) taken during the study (including start and stop dates, dosage, and routes of administration, if known).
- Subjects general health and medical condition upon completion of, or withdrawal from, the study.

11.9 Device Accountability

Per EN ISO 14155-2011, the investigational devices/equipment shall be controlled and used only in this clinical study and according to this CIP/ protocol. Tracking of subjects and device allocations will be performed during the study. The investigational devices, the AcQBlate FORCE catheter, the Qubic RF Generator, and the Qiona Irrigation Pump with Tubing Set will be labeled "For Investigational Use Only" and must be stored in a locked location and away from commercial product.

The Sponsor keeps records to document the physical location of all investigational devices from shipment of investigational devices to the clinical study sites until usage, disposal or return. A device accountability log may be used for the documentation of the process.

Access to investigational devices is controlled and the devices are used in the clinical investigation only and according to the CIP/protocol.

The Investigator or an authorized designee shall keep records documenting the receipt, usage, return, and disposal of the investigational devices including the following:

- Date of receipt,
- Identification of each investigational device/piece of equipment (batch number or unique code),
- Expiry date, as applicable,
- Date or dates of use,
- Subject identification,
- Date of return of unused, expired, or malfunctioning investigational devices/equipment, if applicable.

11.10 Electronic Case Report Forms

This study will use an eCRF as the primary data collection instrument and will record data by electronic capture. All data requested on the eCRF should be entered within two (2) weeks of the data being generated/collected. All missing data must be explained. If a data entry error has been made, the corrected information will be entered on the eCRF. All such changes are recorded in audit reports.

Specific instructions to complete the eCRFs will be provided to the Investigator and other site personnel, as appropriate. The Investigators (and designees) are responsible for reporting clinical study-requested information on the eCRFs.

11.11 Records Retention

The Investigator will retain study essential documents for two (2) years after formal closure or discontinuation of the study. These documents must be retained for a longer period if required by an agreement with Acutus Medical or defined by local or national regulations. Acutus Medical will inform the Investigator/Institution as to the date of formal closure or discontinuation of the study.

11.12 Clinical Monitor

A CRO may be designated as the clinical monitor for this study. Their personnel will be qualified by training and experience to oversee the conduct of the study. The Clinical Monitors responsibilities include maintaining regular contact with each clinical study site through telephone contact or email to ensure that: 1) the CIP/protocol is followed; 2) complete, timely, and accurate data are submitted; 3) problems with inconsistent and incomplete data are addressed; 4) complications and UADEs are reported to the Sponsor; and 5) the site facilities continue to be adequate.

11.13 Clinical Data Monitoring Procedures

Monitoring requirements will be defined in the Clinical Monitoring Plan (CMP). The Clinical Monitors/CRAs (or designees) may conduct site visits at the clinical study sites to monitor the clinical study, which will be in compliance with the CIP/protocol, QAPs, and the CMP. When a site visit is performed, the clinical study site agrees to allow the monitors and other authorized Acutus Medical personnel access to information. The monitors may verify data entered into the eCRFs against hospital/clinic records or other source documents in order to ensure accuracy and completeness of the eCRFs for each subject. Clinical Investigators and their clinical study staff agree to assist the monitors in their activities. Requests may be made to review patient charts by Acutus Medical personnel and/or designee(s) so that CIP/protocol adherence and source documentation can be verified.

Monitoring activities may include, but are not limited to:

- Evaluation of subject screening and selection methods
- Verification of signed ICFs for each subject
- Verification of source documentation against completed eCRFs for each subject
- Assurance that required clinical study reports (CSRs), including reports to the applicable IRB/EC/CA, are generated in a timely manner
- Monitoring of safety events, including device deficiencies that may have led to an SAE
- Monitoring of device deficiencies, irrespective of associated safety events
- Review of CIP/protocol deviations
- Overall clinical study compliance
- Review of the Investigator Site File (ISF)

11.13.1 Medical Monitor

The medical Monitor for the clinical study is:

Jerald L. Cox, PA
Jerry.cox@acutus.com

Phone: +1 760.529-6310

11.14 Investigator Responsibilities

The Investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, 21 CFR, the Declaration of Helsinki, the principles of GCP, International Organization for Standardization (ISO) 14155:2011, applicable regulatory requirements, and institutional procedures.

11.15 Deviations from the Clinical Investigational Plan/Protocol

A CIP/protocol deviation is defined as an event in which the Investigator or site personnel deviates from the clinical study protocol or clinical study procedures. It is the Investigator's responsibility to ensure that there are no deviations from the CIP/protocol. Waivers for CIP/protocol deviations are prohibited.

An Investigator may deviate from the CIP/protocol without prior written approval from Acutus Medical in cases of medical emergencies to protect the life or physical well-being of a subject. In the event of an emergent deviation, the Investigator is required to notify Acutus Medical and the applicable IRB/EC/CA/FDA as soon as possible, but no later than five (5) business days from the occurrence of the deviation from the CIP/protocol.

Except in such an emergency, prior approval by Acutus Medical is required for changes in, or deviations from, the CIP/protocol. Additionally, if these changes or deviations affect the scientific soundness of the CIP/protocol or the rights, safety, or welfare of human subjects, IRB/EC/CA/FDA notification is required.

Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control (e.g., the subject was not available for a scheduled follow-up office visit or has moved without providing a forwarding address). These events, although outside the Investigator's control, are still required to be reported on the appropriate Protocol Deviation eCRF in order to ensure that all deviations from the standard subject population are adequately documented and reported. The Investigator will inform Acutus Medical of all CIP/protocol deviations.

If Acutus Medical becomes aware that an Investigator is not complying with the any part of the CIP/protocol, including the signed Investigator Agreement (IA), the CIP/protocol, or any conditions of approval imposed by the reviewing IRB/EC/CA, Acutus Medical will immediately secure compliance, and may suspend the Investigator's participation (including enrollment at the site). Acutus Medical may terminate an Investigator's participation in the clinical study at its discretion.

11.15.1 Maintaining Records

The Investigator will maintain the following accurate, complete, and current records related to the Investigator's participation:

- Correspondence with another Investigator, an IRB/EC/CA, Acutus Medical, a Sponsor monitor or designee, or any regulatory agency.
- Records of each patient's case history and exposure to the device, including:
  - Documents evidencing ICF and for participation in the clinical study without informed consent,
  - Any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain ICF,
  - All relevant observations, including records concerning adverse device effects (whether anticipated or not),
  - Information and data on the condition of each subject upon entering, and during the course of the clinical study, including information related to relevant previous medical history and the results of all diagnostic tests,
- Protocol deviations, with documents showing the dates of and reasons for each deviation from the CIP/protocol.

11.15.2 Submitting Reports

In compliance with local and national laws, each Investigator may be required to prepare and submit complete, accurate, and timely reports to Acutus Medical and/or IRBs/ECs/CAs. These reports may include:

- Any UADE occurring during a clinical study.
- Any deviation from the CIP/protocol made to protect the life or physical well-being of a subject in an emergency.
- Any further information requested by an IRB/EC/CA about any aspect of the clinical study.

The Investigator will provide, in writing, any withdrawal of IRB/EC/CA approval of the study or an Investigator within five (5) business days of such action.

11.15.3 Clinical Study Report and Publication of Data

Within one (1) year of the close of the clinical database a clinical study report (CSR) will be provided to the Investigator for input and review. The report will be signed by Acutus Clinical Affairs, and all Investigators and a finalized copy will be stored at the clinical study site.

Acutus Medical is committed to the dissemination of clinical study results. Any publication related to the AcQBlate Force clinical study will require the identification of Acutus Medical as Sponsor.

11.16 Acutus Medical Responsibilities

11.16.1 General Duties

Acutus Medical has the overall responsibility for the conduct of the clinical study, including assurance that the clinical study satisfies the regulatory requirements of the appropriate regulatory agencies, ensuring IRB/EC/CA/FDA approvals, selecting Investigators, ensuring proper monitoring and that ICF is obtained. Acutus Medical will provide all information necessary to conduct the clinical study, including the CIP/protocol and any reports of prior investigations, as appropriate. During the conduct of the clinical study, updates regarding information that may impact the clinical study will be made available to all appropriate national and local regulatory authorities.

11.16.2 Selection of Investigators

Acutus Medical will select Investigators (including Sub Investigators performing the procedure) qualified by training and experience. Sites will be selected based on a site assessment, appropriate facilities, clinical experience, and the qualifications of the Principal Investigator (PI) (also known as the Investigator). Investigators will be evaluated by Acutus Medical based on:

- Curriculum vitae, or other statement of Investigator's relevant training and experience, including type of experience with the intended procedure and clinical study, specifically.
- Education and experience in the ablation management of arrhythmias.
- Whether the Investigator has an adequate patient population to meet requirements of the clinical study enrollment.
- Whether the Investigator has adequate time to be personally involved in the conduct of the clinical study, and adequate clinical study staff and resources to support the clinical study.
- Whether the Investigator's clinical study center is associated with an IRB/EC that satisfies all applicable regulatory requirements.
- Whether an Investigator was involved in an investigation or other clinical study that was terminated. This may require an explanation of the circumstances that led to the termination.

Prior to clinical study initiation, each Investigator must also submit a:

- Certificate of human patient's protection training (if required by the reviewing IRB/EC),
- Signed Investigator's Agreement, indicating an Investigator's commitment to:
  - Conduct the clinical study in accordance with the agreement, the CIP/protocol, CFRs, GCP, and any conditions of approval imposed by the IRB/EC;
  - Supervise all testing of the device involving human subjects;
  - Ensure that the requirements for informed consent are met;
  - Conduct the clinical study according to the CIP/protocol.

The Sponsor reserves the right to apply additional criteria to site and/or Investigator selection.

11.17 Training

Acutus Medical will provide training on the AcQBlate Force Sensing System prior to enrolling any subject. Training may consist of a review of the IFU, hands-on training on the device and procedure, presentations, literature, etc. Additional training will include a review of the protocol, the regulations for medical device investigations, and general clinical study logistics required to complete the clinical study.

Training of appropriate clinical study staff will be the responsibility of Acutus Medical (or designee). To ensure uniform data collection and protocol compliance, training will include a review the CIP/protocol (including the ICF), techniques for identification of eligible subjects,

instructions on data collection, methods for scheduling follow-up visits in the window, etc. Detailed feedback regarding completion of the eCRFs, clinical study requirements, and protocol compliance will be provided by Acutus Medical, its study monitors, and/or designees functioning in a data management capacity.

11.17.1 Role of Representative

Acutus Medical may provide technical support to the Investigators and other health care personnel (collectively HCP) as needed during the conduct of the clinical study. Support may include training, addressing questions, or providing clarifications concerning the operation of Acutus Medical products or the procedures and forms related to the CIP/protocol.

At the request of the Investigator and while under their supervision, Acutus Medical personnel may be requested to provide assistance with technical support or other activities during the AcQForce procedure. Typical tasks may include:

- Clarifying device behavior, operation or diagnostic output as requested by the Investigator or other health care personnel,
- Assisting with the collection of study data from the AcQBlate Force Sensing System during the procedure,
- Recording data on study worksheets (as long as the responsible site staff verified and signed the completed worksheet).

Acutus Medical and industry representatives do not practice medicine; provide medical diagnosis or treatment to patients; discuss a patient's condition or treatment with a patient without the approval and presence of the site study staff; independently collect critical study data (defined as primary or secondary endpoint data), or enter data in electronic data capture systems.

11.17.2 Changes in the Clinical Investigational Plan/Protocol

Acutus Medical will obtain appropriate regulatory approval for any change to the CIP/protocol that may affect the scientific soundness of the clinical study or the rights, safety, and/or welfare of the subjects.

Acutus Medical will provide approved protocol amendments to the Investigators prior to implementing the amendment. The Investigator will be responsible for notifying the reviewing IRB/EC and CA (if applicable) of the protocol amendment (administrative changes) or obtaining IRB/EC/CA approval of the protocol amendment (changes in subject care or safety), according to the instructions provided with the protocol amendment. The IRB/EC/CA/FDA acknowledgement/approval of the protocol amendment must be documented in writing prior to implementation of the protocol amendment. Copies of this documentation must be provided to Acutus Medical and placed in the Trial Master File (TMF).

11.17.3 Withdrawal of Regulatory Approval

Acutus Medical will notify all reviewing IRBs/ECs/CAs and participating Investigators of any withdrawal of regulatory approval to conduct the clinical study and shall do so within five (5) business days after receipt of notice of the withdrawal of approval.

12 FINANCIAL OBLIGATIONS

The AcQForce Flutter clinical study is financed by Acutus Medical, Inc. A financial agreement will be established with the clinical study site delineating contracted prices for all clinical study services.

13 ETHICS AND REGULATORY COMPLIANCE

13.1 Conduct of the Clinical Study

Conduct of the clinical study will follow QAPs from Acutus Medical, as well as the Code of Federal Regulations (CFRs), Declaration of Helsinki, GCPs, EN ISO 14155:2011, and other regional and local laws. Each Investigator must sign and date the IA prior to the start of this clinical study. With the signature, the Investigator agrees to perform all clinical study procedures according to the governing local and national regulations and the CIP/protocol.

13.2 Institutional Review Board/Ethics Committee Approval

A properly constituted, valid IRB/EC must review and approve the CIP/protocol, ICF, and related patient information and recruitment materials prior to initiation of the clinical study. It is the responsibility of the Investigator and/or Sponsor to obtain protocol approval from the institution's IRB/EC, and to keep the IRB/EC informed of any SAEs or SADEs and amendments to the protocol. Additional requirements imposed by the IRB/EC or other regulatory authority shall be followed as appropriate. All correspondence with the IRB/EC should be filed by the Investigator and copies sent to Acutus Medical (or designee).

13.3 Competent Authority Approval

For European clinical study sites, it is the responsibility of the Sponsor to obtain protocol approval from the country's Competent Authority, and to keep the CA informed of any SAEs or SADEs and amendments to the protocol. Additional requirements imposed by the CA or other regulatory authority shall be followed as appropriate. All correspondence with the CA should be filed in the TMF.

13.4 Clinical Study Informed Consent Approval

In accordance with the principles of Informed Consent, 21 CFR Part 50, the Declaration of Helsinki, GCP, and EN ISO 14155:2011, ICF will be obtained and documented in writing before a patient is enrolled in the clinical study.

It is the responsibility of the Investigator to ensure that a written ICF is obtained from the subject (or legally acceptable representative) before any activity or procedure is undertaken that is not part of routine care. Information obtained during the conduct of the clinical study that may impact the patient ICF may require revisions to the ICF. If so, revisions and approvals of such changes by the appropriate regulatory authority is required. Documentation of the current versions of the informed consent will be documented in the clinical study TMF.

13.5 Identification and Confidentiality

Subject identification and confidentiality will be ensured in accordance with all applicable regulatory and IRB/EC governance. This includes, but is not limited to, the following:

- Subjects will be identified on all eCRFs and source documents by a unique anonymized identification reference number.
- eCRFs are confidential documents and will only be made available to Acutus Medical (and appropriate designees), the Investigator, the biostatistician, and, if requested, to advisory committees and regulatory authorities (including the FDA).
- Data will be stored in accordance with regulations for handling of electronic data.

The site will maintain (anonymous to Acutus Medical) a list identifying all subjects entered into the clinical study. The list will be maintained as part of the Investigator Site File (ISF) file and monitored for completeness.

13.6 Site Qualification Visits

A Site Qualification Visits (SQV) will follow Acutus Medical QAPs.

13.7 Site Initiation Visits

All clinical study personnel will be required to participate in a Site Initiation Visit (SIV) that follows Acutus Medical's QAP. Portions of the SIV training may be completed via a web access meeting. Components of this initiation visit may include:

- Introduction of the clinical study design including the protocol-specific treatment and follow-up phase
- ICF process

- Product training to all end-users
- eCRF completion training
- Safety reporting instructions
- Training on the regulations governing human research
- Procedure training on the use of the device

13.8 Insurance

Acutus Medical shall maintain insurance coverage for this clinical study. Pertinent information regarding the coverage shall be made available to the site upon request.

13.9 Site Audit Plan

Participation as an Investigator in this clinical study implies acceptance of potential inspection by government regulatory authorities and applicable compliance and quality assurance offices. The Investigator and/or designee must be available to respond to reasonable requests and queries made by authorized regulatory representatives during the audit process. The Investigator must provide Acutus Medical with copies of all correspondence that may affect the review of the current clinical study or their qualifications as an Investigator in this and future clinical studies conducted by Acutus Medical.

13.9.1 Site Data Audits by Acutus Medical

In accordance with local and national regulations and Acutus Medical's QAPs, an internal audit may be requested to access all clinical study records, including source documents, for inspection and duplication. The Investigator will ensure the capability for inspections of applicable clinical study-related functions.

A site data quality assurance audit may be conducted during the clinical study.

13.9.2 External Audits

Requests by regulatory agencies to inspect the clinical study sites may be made as well. The Investigator and/or designee is required to report to Acutus Medical as soon as possible after receiving a request from a regulatory authority to perform an audit. The clinical Investigator agrees to allow inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

13.10 Public Domain Access to the Clinical Study

A description of this clinical study will be available on http//www.Clinicaltrials.gov. Information regarding the public access will be presented in the ICF.

13.11 Required Reports

Acutus Medical will remain in compliance with all required and pre-specified reports during the enrollment and follow-up of the clinical study. IRB/EC/CA requirements for reports will be provided as requested.

14 GENERAL CONSIDERATIONS

14.1 Discontinuation of the Clinical Study

The Sponsor reserves the right to discontinue the clinical study at any stage, with suitable written notice to the Investigator and the appropriate government regulatory agencies. Similarly, Investigators may withdraw from the study, subject to providing written notification to the Sponsor within thirty (30) days of their intent to withdraw. However, the Sponsor and Investigators will be bound by their obligation to complete the follow-up of subjects already enrolled into the clinical study.

Acutus Medical, as Sponsor, may terminate Investigator and site participation in the clinical study if there is evidence of an Investigator's failure to maintain adequate clinical standards or evidence of an Investigator's or staff's failure to comply with the CIP/protocol/or IA.

Notification of suspension or termination will occur no later than five (5) business days after Acutus Medical makes the determination. In the event of clinical study suspension or termination, Acutus Medical or designee will send a report outlining the circumstances to the reviewing IRB/EC/CA, the appropriate regulatory agencies, and to all participating Investigators. Any suspension or termination may not be re-initiated without prior approval of the IRB/EC/CA and Acutus Medical.

14.2 Use of Information and Publications

All information concerning Acutus Medical operations, patent applications, manufacturing processes, and basic scientific data supplied by Acutus Medical to the Investigator and not previously published, are considered confidential and remain the sole property of Acutus Medical. This includes all clinical study materials, worksheets, and eCRFs.

The information developed in this clinical study may be used by Acutus Medical as support for a regulatory filing and in connection with the continued development of the AcQBlate Force Sensing System. Any publication or other public presentation of the data resulting from this clinical study will require prior review and written approval of Acutus Medical.

At the conclusion of the clinical study, it is expected that Acutus Medical and the Investigators will promptly prepare and submit a manuscript for publication in a reputable scientific journal.

Further analyses, beyond those presented in the initial publication may be proposed to Acutus Medical. For purposes of timely abstract presentation and publication, such secondary

publications may be delegated to the appropriate principal authors; however, final analyses and manuscript review for data will require the prior written approval of Acutus Medical.

None of the results, in whole or part, of the clinical study carried out under this CIP/protocol, nor any of the information provided by Acutus Medical for the purposes of performing the clinical study, will be published or passed on to any third party without the consent of Acutus Medical. Any Investigator involved with this clinical study is obligated to provide Acutus Medical with complete test results and all data derived from the clinical study.

15 REFERENCES

1. Page RL, Joglar JA, Caldwell MA, et al. 2015 ACC/AHA/HRS Guideline for the Management of Adult Patients With Supraventricular Tachycardia: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm. *J Am Coll Cardiol*. 2016;67(13):1575-1623. doi:10.1016/j.jacc.2015.09.019
2. Wellens HJJ. Contemporary management of atrial flutter. *Circulation*. 2002;106(6):649-652. doi:10.1161/01.CIR.0000027683.00417.9A
3. Saoudi N, Cosío F, Waldo A, et al. A classification of atrial flutter and regular atrial tachycardia according to electrophysiological mechanisms and anatomical bases: A statement from a joint expert group from the working group of arrhythmias of the European society of cardiology and the . *Eur Heart J*. 2001;22(14):1162-1182. doi:10.1053/euhj.2001.2658
4. Granada J, Uribe W, Chyou PH, et al. Incidence and predictors of atrial flutter in the general population. *J Am Coll Cardiol*. 2000;36(7):2242-2246. doi:10.1016/S0735-1097(00)00982-7
5. Orejarena LA, Vidaillet H, Destefano F, et al. Paroxysmal supraventricular tachycardia in the general population. *J Am Coll Cardiol*. 1998;31(1):150-157. doi:10.1016/S0735-1097(97)00422-1
6. Wann LS, Curtis AB, January CT, et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline): A report of the american college of cardiology foundation/American heart association task force on practice guidelines. *J Am Coll Cardiol*. 2011;57(2):223-242. doi:10.1016/j.jacc.2010.10.001
7. Glover BM, Chen J, Hong KL, et al. Catheter ablation for atrial flutter: A survey by the European heart rhythm association and canadian heart rhythm society. *Europace*. 2016;18(12):1880-1885. doi:10.1093/europace/euw402
8. Bun S, Latcu G, Wedn AM, Hasni K, Saoudi N. Cavotricuspid isthmus-dependent atrial fl utter : clinical perspectives. *Res Reports Clin Cardiol*. 2019;10:7-17.
9. Spector P, Reynolds MR, Calkins H, et al. Meta-Analysis of Ablation of Atrial Flutter and Supraventricular Tachycardia. *Am J Cardiol*. 2009;104(5):671-677. doi:10.1016/j.amjcard.2009.04.040
10. Demazumder D, Mirotznik M, Schwartzman D. Biophysics of Radiofrequency Ablation using an Irrigated Electrode. *J Interv Card Electrophysiol*. 2001;5(4):377-389. doi:10.1016/j.physbeh.2017.03.040
11. Sacher F, O'Neill MD, Jais P, et al. Prospective randomized comparison of 8-mm gold-tip, externally irrigated-tip and 8-mm platinum-iridium tip catheters for cavotricuspid isthmus ablation. *J Cardiovasc Electrophysiol*. 2007;18(7):709-713. doi:10.1111/j.1540-8167.2007.00861.x
12. Da Costa A, Faure E, Thévenin J, et al. Effect of isthmus anatomy and ablation catheter on radiofrequency catheter ablation of the cavotricuspid isthmus. *Circulation*.

2004;110(9):1030-1035. doi:10.1161/01.CIR.0000139845.40818.75

13. Shimizu Y, Yoshitani K, Murotani K, et al. The deeper the pouch is, the longer the radiofrequency duration and higher the radiofrequency energy needed—Cavotricuspid isthmus ablation using intracardiac echocardiography. *J Arrhythmia*. 2018;34(4):410-417. doi:10.1002/joa3.12075

14. Jaïs P, Shah DC, Haïssaguerre M, et al. Prospective randomized comparison of irrigated-tip versus conventional- tip catheters for ablation of common flutter. *Circulation*. 2000;101(7):772-776. doi:10.1161/01.CIR.101.7.772

15. Zei PC, Hunter TD, Gache LM, O'Riordan G, Baykaner T, Brodt C. Low-fluoroscopy atrial fibrillation ablation with contact force and ultrasound technologies: a learning curve. *Pragmatic Obs Res*. 2019;Volume 10:1-7. doi:10.2147/por.s181220

16. Haines DE. Determinants of Lesion Size During Radiofrequency Catheter Ablation: The Role of Electrode-Tissue Contact Pressure and Duration of Energy Delivery. *J Cardiovasc Electrophysiol*. 1991;2(6):509-515. doi:10.1111/j.1540-8167.1991.tb01353.x

17. Yokoyama K, Nakagawa H, Shah DC, et al. Novel contact force sensor incorporated in irrigated radiofrequency ablation catheter predicts lesion size and incidence of steam pop and thrombus. *Circ Arrhythm Electrophysiol*. 2008;1(5):354-362. doi:10.1161/CIRCEP.108.803650

18. Weiss, Christian, Antz, Matthias, Eick, Olaf, Eshagzaiy, Kablai, Meinertz, Thomas, Willems S. Radiofrequency catheter ablation using cooled electrodes: impact of irrigation flow rate and catheter contact pressure on lesion dimensions. *PACE - Pacing Clin Electrophysiol*. 2002;25(4):463-469.

19. Okumura Y, Johnson SB, Bunch TJ, Henz BD, O'Brien CJ, Packer DL. A systematical analysis of in vivo contact forces on virtual catheter tip/tissue surface contact during cardiac mapping and intervention. *J Cardiovasc Electrophysiol*. 2008;19(6):632-640. doi:10.1111/j.1540-8167.2008.01135.x

20. Reddy VY, Shah D, Kautzner J, et al. The relationship between contact force and clinical outcome during radiofrequency catheter ablation of atrial fibrillation in the TOCCATA study. *Hear Rhythm*. 2012;9(11):1789-1795. doi:10.1016/j.hrthm.2012.07.016

21. Kuck KH, Reddy VY, Schmidt B, et al. A novel radiofrequency ablation catheter using contact force sensing: Toccata study. *Hear Rhythm*. 2012;9(1):18-23. doi:10.1016/j.hrthm.2011.08.021

22. Natale A, Reddy VY, Monir G, et al. Paroxysmal AF catheter ablation with a contact force sensing catheter: Results of the prospective, multicenter SMART-AF trial. *J Am Coll Cardiol*. 2014;64(7):647-656. doi:10.1016/j.jacc.2014.04.072

23. Neuzil P, Reddy VY, Kautzner J, et al. Electrical reconnection after pulmonary vein isolation is contingent on contact force during initial treatment: Results from the EFFICAS i study. *Circ Arrhythmia Electrophysiol*. 2013;6(2):327-333. doi:10.1161/CIRCEP.113.000374

24. Kumar S, Morton JB, Lee G, Halloran K, Kistler PM, Kalman JM. High incidence of low catheter-tissue contact force at the cavotricuspid isthmus during catheter ablation of atrial

flutter: Implications for achieving isthmus block. *J Cardiovasc Electrophysiol*. 2015;26(8):826-831. doi:10.1111/jce.12707

25. Venier S, Andrade JG, Khairy P, et al. Contact-force-guided vs. contact-force-blinded catheter ablation of typical atrial flutter: A prospective study. *Europace*. 2017;19(6):1043-1048. doi:10.1093/europace/euw137

26. Gould PA, Booth C, Dauber K, Ng K, Claughton A, Kaye GC. Characteristics of Cavotricuspid Isthmus Ablation for Atrial Flutter Guided by Novel Parameters Using a Contact Force Catheter. *J Cardiovasc Electrophysiol*. 2016;27(12):1429-1436. doi:10.1111/jce.13087

27. Brugada J, Katritsis DG, Arbelo E, et al. 2019 ESC Guidelines for themanagement of patients with supraventricular tachycardia. *Eur Heart J*. 2020;41(5):655-720. doi:10.1093/eurheartj/ehz467

ACUTUS Medical

AcQBlate Force Sensing Ablation System US IDE and EU Study for Atrial Flutter (AcQForce Flutter & AcQForce Flutter-EU)

Study CLP-21, Rev 12
Study CLP-21-EU, Rev 03

Statistical Analysis Plan

Version 2.0, 15Mar2022

Version History

Version	Version Date	Author/Title	Summary of Key Changes
1.0	8Feb2022	Lindsay Lucas/ Senior Biostatistician	Initial Release
2.0	15Mar2022	Lindsay Lucas/ Senior Biostatistician	Minor change made to Section 6.2.4 per FDA recommendation

Table of Contents

1 Introduction

This statistical analysis plan (SAP) describes the planned statistical methods for the reporting and analysis of data collected under the Clinical Investigation Protocol AcQBlate Force Sensing Ablation System US IDE for Atrial Flutter (AcQForce Flutter) (CLP-21) and Clinical Investigation Protocol AcQBlate Force Sensing Ablation System EU Study for Atrial Flutter (AcQForce Flutter-EU) (CLP-21-EU). Data from these studies will be used to support a pre-market approval (PMA) application.

This SAP should be read in conjunction with the study clinical investigation plan (CIP) and case report forms (CRFs). This version of the SAP has been developed with respect to the Clinical Investigation Protocol AcQBlate Force Sensing Ablation System US IDE for Atrial Flutter (AcQForce Flutter) Rev 12 19Oct2021 and Clinical Investigation Protocol AcQBlate Force Sensing Ablation System EU Study for Atrial Flutter (AcQForce Flutter-EU) Rev 02 21May2021. Any revisions to the protocols or CRFs that impact the planned analyses may require updates to the SAP.

Applicable Documents:

Document Number, Version	Document Title
CLP-21, Rev 12	Clinical Investigation Plan for AcQBlate Force Sensing Ablation System US IDE for Atrial Flutter (AcQForce Flutter)
CLP-21-EU, Rev 03	Clinical Investigation Plan for AcQBlate Force Sensing Ablation System EU Study for Atrial Flutter (AcQForce Flutter-EU)
CLP-21-DE Rev 01	Clinical Investigation Plan for AcQBlate Force Sensing Ablation System DE Study for Atrial Flutter (AcQForce Flutter-DE)
QAP 3.8	Quality Assurance Procedure for Clinical Studies

2 Abbreviations

Abbreviation/Term	Definition
AAD	Antiarrhythmic drug
AE	Adverse Event
ASD	Atrial Septal Defect

BDB	Bidirectional Block
CIP	Clinical Investigational Plan
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CTI	Cavotricuspid Isthmus
DCCV	Direct Current Cardioversion
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ICD	Implantable Cardioverter Defibrillator
IDE	Investigational Device Exemption
ITT	Intention-to-Treat
mITT	Modified Intention-to-Treat
OUS	Outside of United States
PFO	Patent Foramen Ovale
PMA	Premarket Approval
PPT	Pre-procedure Testing
RF	Radiofrequency
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SSED	Safety and Effectiveness Data
TIA	Transient Ischemic Attack
US	United States

3 Clinical Study Objective

The objective is to demonstrate that the AcQBlate Force Sensing System is safe and effective when used to ablate the cavotricuspid isthmus (CTI) for the treatment of typical atrial flutter when compared to a literature-based control.

Data will be used to support a PMA application.

4 Study Design

The AcQForce Flutter and AcQForce Flutter-EU clinical studies are prospective, multi-center, non-randomized, global clinical studies designed to confirm the safety and efficacy of the AcQBlate Force Sensing System. All subjects with typical atrial flutter will undergo percutaneous catheter ablation of the cavotricuspid isthmus using the AcQBlate Force Sensing System with the endpoint of achieving bidirectional block (BDB). Treated subjects will have data collected at screening, procedure, pre-hospital discharge, and 7-and 30-days post procedure. The subject population will consist of men and women 18 years of age or older, presenting for a *de novo* percutaneous cardiac ablation of the cavotricuspid isthmus for typical atrial flutter.
De

5 Statistical Analyses

5.1 General Considerations

Except where otherwise specified, the following general principles apply to the planned statistical analyses. All statistical analysis will be conducted using SAS software version 9.3 or later or other widely accepted statistical or graphical software as required.

5.1.1 Descriptive Statistics

Continuous variables will be summarized as means, standard deviations, medians, and ranges. Categorical variables will be summarized as frequencies and percentages.

Confidence intervals may be presented, where appropriate, using the t-distribution for continuous data and Clopper-Pearson Exact method for categorical variables.

5.1.2 Study Day

Study day 0 is the date of the index procedure. Day in study will be calculated relative to the index procedure as follows:

Study Day = Assessment Date – Index Procedure Date

For each subject, duration in study will be based on last study contact date which is the latest date of all follow-up visits, assessments, adverse event onset or resolution, and study exit including date of death.

Duration variables will be calculated as follows:

Duration Days = End Date – Start Date

5.1.3 Visit Windows

Unless otherwise specified, visit based assessments will be analyzed for each analysis time point according to the nominal visit entered in the Case Report Form (CRF) regardless of if it is out of window.

5.1.4 Statistical Significance

Confidence intervals and statistical tests will be performed at a two-sided 5% significance level unless specified otherwise. P-values will be rounded to four decimal places. If a p-value is less than 0.001 it will be reported as "<0.001".

5.1.5 Precision

Unless otherwise specified, the following conventions will apply for data display. In general, percentages will be displayed to 1 decimal place. Percentages <0.05% will be reported to 2 decimal places.

5.2 Analysis Populations

The following analysis populations are defined for analysis:

1. The **Enrolled Analysis Set** will consist of subjects who have signed an informed consent form, are deemed study eligible by meeting all of the inclusion and none of the exclusion criteria up to the point of the procedure.
2. The **Pre-procedure Testing (PPT) Failure Set** will consist of enrolled subjects who have presented for the procedure in any rhythm other than sinus rhythm or typical atrial flutter and have not undergone venous access. These subjects will be treated per the recommendations of the study physician and exited from the study. No use of the investigational device is allowed. A Study Exit electronic case report form (eCRF) will be completed.
3. The **Intention-to-Treat (ITT) Failure Analysis Set** will consist of enrolled subjects who have the venous access portion of the ablation procedure initiated, regardless of whether the AcQBlate FORCE Catheter has been inserted, and up to the point of completion of the right-atrial access but prior to any RF application with the

investigational device. The ITT Failure subjects will be followed for safety reasons through the 7-day follow-up visit. All ITT Failure subjects will be excluded from any efficacy data analysis. In addition to the Discharge eCRF and the 7-day Follow-up eCRF, a Study Exit eCRF will also be completed. The ITT Failure population may include:

- At the time of the procedure, if the subject does not demonstrate conduction through cavotricuspid isthmus, the subject will be exited from the study and followed for safety through the 7-day follow-up visit.
- At the time of procedure, if atrial fibrillation is initiated during the process of inducing typical AFL, a direct current cardioversion (DCCV) may be performed to attempt conversion to sinus rhythm so that the CTI conduction portion of the study may proceed. If during confirmation of the CTI conduction, the investigator determines that further ablation beyond the CTI is warranted the subject will be exited from the study and followed for safety through the 7-day follow-up visit.

4. The **Modified Intention-to-Treat (mITT) Analysis Set** will consist of enrolled subjects who initiates the ablation procedure using the AcQBlate Force Sensing System. An initiated ablation procedure is defined as a procedure where the AcQBlate Force Sensing System is used for the ablation procedure irrespective if a non-investigational device was used to complete the ablations. mITT subjects will be followed for all study outcome measures for the full duration of the clinical study and will comprise the data set for the Primary Efficacy Endpoints.

5.3 Handling of Missing Data

All attempts will be made to limit the amount of missing data. Unless otherwise specified, no attempt will be made to impute missing data. If a data point is missing, that data point will not contribute to that portion of the analysis. The number of evaluable observations will be reported in analysis so that extent of missing data can be assessed. Sensitivity analyses will be performed for the primary safety and efficacy endpoints as detailed in Section 6.6.

5.4 Subject Disposition

The number of subjects in each analysis population will be presented along with reason for any exclusions. Subject accountability will be summarized by visit. The number of subjects who are enrolled, eligible for follow-up, and number completing clinical follow-up will be summarized for each protocol-required visit. In addition, the number of subjects who complete the study or exit early will be summarized by reason.

5.5 Demographics and Baseline Characteristics

Demographics, baseline data, including but not limited to relevant descriptors from the medical history, co-morbidities, and medications, will be summarized.

Procedural data collection will also be analyzed and summarized.

5.6 Analysis of Study Endpoints

5.6.1 Primary Safety Endpoint

The primary safety endpoint is defined as the proportion of mITT and select ITT Failure subjects (i.e., subjects who had the AcQBlate FORCE Catheter inserted) who are free from a composite list of pre-specified device/procedure related SAEs that occur through 7-days post ablation procedure. Subjects who do not have evidence of a SAE/SADE from the composite list of safety events will be considered a success.

Serious adverse events that meet the definition for Primary Safety Endpoint are pre-defined and include:

- Death
- Cardiac tamponade/perforation
- Myocardial infarction
- Stroke
- Systemic embolism
- Major access site complications
- Major bleeding requiring transfusion
- Complete heart block
- Other SAEs/SADEs adjudicated by an independent review as “probably or definitely related” to the Investigational device.

5.6.1.1 Primary Safety Endpoint Analysis

The null and alternate hypotheses for primary safety endpoint are as follows:

Ho: The proportion of mITT subjects and select ITT Failure subjects (ρ) who are free from device/procedure related SAE through 7-days post ablation procedure is less than or equal to 93.0%.

$$Ho: \rho \leq 93.0\%$$

Ha: The proportion of mITT and select ITT Failure subjects (ρ)who are free from device/procedure related SAE through 7-days post ablation procedure is greater than 93.0%.

$$Ha: \rho > 93.0\%$$

The null hypothesis will be rejected if the one-sided 95% Clopper-Pearson Exact lower confidence bound is greater than 93.0%.

5.6.1.2 Sensitivity Analysis

Sensitivity analyses to assess the effect of missing data on the primary safety endpoint will be performed including:

- A tipping point analysis in which missing data are varied from worst case to best case to evaluate mITT and ITT Failure subjects with missing primary safety data.

5.6.2 Primary Efficacy Endpoint

The primary efficacy endpoint is defined as the proportion of mITT subjects (β) achieving acute procedural success. Acute procedural success is defined as the demonstration of bidirectional cavotricuspid isthmus block confirmed at least 20 minutes following the last radiofrequency (RF) application at the cavotricuspid isthmus with the investigational catheter.

5.6.2.1 Primary Efficacy Endpoint Analysis

The null and alternate hypotheses for primary efficacy endpoint are as follows:

Ho: The proportion of mITT subjects (β) demonstrating bidirectional cavotricuspid isthmus block confirmed at 20 minutes following the last right atrial radiofrequency (RF) application at the cavotricuspid isthmus with the investigational catheter is less than or equal to 83.7%.

Ho: $\beta \leq 83.7\%$

Ha: The proportion of mITT subjects (β) demonstrating bidirectional cavotricuspid isthmus block confirmed at 20 minutes following the last right atrial radiofrequency (RF) application at the cavotricuspid isthmus with the investigational catheter is greater than 83.7%.

Ha: $\beta > 83.7\%$

The null hypothesis will be rejected if the one-sided 95% Clopper-Pearson Exact lower confidence bound is greater than 83.7%.

A primary efficacy failure will comprise the following:

- The inability to achieve and maintain bidirectional CTI block at least 20 minutes following the last RF application with the investigation device. A second investigative catheter or alternate AcQBlate FORCE catheter curve may be used prior to designation as failure. Maximum RF time before considering a non-investigational catheter is at the discretion of the Investigator but shall not exceed 60 minutes of RF time.
  OR
- The use of a commercially available non-investigational catheter for any ablation of the CTI.

NOTE: Use of isoproterenol is at the discretion of the Investigator.

5.6.2.2 Sensitivity Analysis

Sensitivity analyses to assess the effect of missing data on the primary efficacy endpoint will be performed including:

- A tipping point analysis in which missing data are varied from worst case to best case to evaluate subjects with missing primary efficacy data in the mITT analysis set.

5.6.3 Other Safety Analyses

Adverse events (AE) will be reported for all mITT and ITT Failure subjects.

Individual device/procedure related SAEs at 7-days will be analyzed by event frequencies and proportions of subjects. Total and individual non-serious, device/procedure related AEs at 30-days will also be analyzed by event frequencies and proportion of subjects. Adverse events will be analyzed in terms of their severity, action taken, and duration to resolution.

Device Deficiency Reports will be analyzed for frequencies of safety events and proportion of subjects as part of the safety analyses.

All AEs and SAEs will be tabulated with the number of events and subjects with event for each event type and overall. The rate of all AEs and SAEs reported in the study will be reported as well as the rates at 7 and 30 days. AEs and SAEs will also be summarized by relatedness and severity. Adverse events leading to death or study discontinuation will be provided in listing format. Rates will be reported as the number of subjects who experience at least one event during the analysis interval out of the total number of subjects with follow-up to the beginning of the analysis interval.

5.6.4 Observational Effectiveness Endpoint

The observational effectiveness endpoint, defined as the proportion of mITT subjects free from recurrence of typical CTI dependent atrial flutter OFF Class I/III antiarrhythmic drugs (AADs) at 30-days post index procedure measured by a 24-hour continuous electrocardiogram (ECG) monitor, will be reported with 95% Clopper-Pearson Exact confidence intervals.

5.7 Poolability Analyses

All investigational sites will follow the requirements of a common protocol and standardized data collection procedures and forms. The primary endpoints will be presented separately for each site using descriptive statistics. Poolability of the primary endpoints across investigational sites will be evaluated using a logistic regression model with fixed effect for site. If the p-value for the site effect is below 0.15, additional exploratory analyses will be performed to understand any variations in outcomes by site. Assessment of poolability by geography (US vs. OUS) will also be performed as described for site.

5.8 Subgroup Analyses

Subgroup analyses of the primary safety and efficacy endpoints are exploratory. No labeling claims are planned. Analyses will include mITT and ITT Failure subjects for the primary safety endpoint and mITT subjects for the primary efficacy endpoints.

A Pearson chi-squared test or Fisher's exact test will be performed for any significant differences between gender, ethnicity, race and individual co-morbidities and logistic regression will be performed for age. The following comorbidities will be included:

- Diabetes Mellitus
- Coronary Artery Disease
- Hypertension
- Cardiomyopathy (ischemic, non-ischemic)
- Valvular Disease (moderate or severe)
- Congenital Heart Disease
- Patent Foramen Ovale (PFO) or Atrial Septal Defect (ASD)
- Pacemaker or Implantable Cardioverter Defibrillator (ICD)
- Peripheral Vascular Disease
- Stroke, TIA, Systemic Embolic Event
- Coagulopathies (Bleeding Disorders)
- Asthma or other chronic lung disease (except COPD)
- Chronic Obstructive Pulmonary Disease (COPD)
- Renal Dysfunction/Chronic Renal Disease
- Obstructive Sleep Apnea
- Anemia

5.9 Interim Analyses

No interim analyses are planned.

5.10 Protocol Deviations

Deviations from the procedures outlined in the CIP will be reported by investigational sites on the CRF. Protocol deviations will be summarized for all deviations with event counts and number of subjects with at least one deviation.

6 Changes from Planned Analyses

Any changes to planned statistical analyses determined necessary prior to performing the analyses will be documented in an amended Statistical Analysis Plan and approved prior to the analysis when possible. Any other deviations or changes from the planned analyses deemed necessary due to violation of critical underlying statistical assumptions, data characteristics, or missing data will be clearly described in the clinical study report with justification and rationale.

7 Subject Listings

Subject listings will be provided for the primary endpoints, observational effectiveness endpoint, and baseline and procedural data.