Medtronic

ARCTIC FRONT ADVANCE™ 2AF234, 2AF284

Cardiac Cryoablation Catheter

Technical Manual

! USA **Caution:** Federal law (USA) restricts this device to sale by or on the order of a physician.

Explanation of symbols

The following list of symbols and abbreviations applies to various products. Refer to the package labels to see which symbols apply to this product.

LOT	Lot number
REF	Reorder number
	Use-by
STERILE EO	Sterilized using ethylene oxide
	Do not re-use
2 STERILIZE	Do not resterilize
	Do not use if package is damaged
	Package contents
	Cardiac Cryoablation Catheter
	Consult instructions for use
	Fragile, handle with care
	Keep dry
	Product documentation
	Humidity limitation
	Storage temperature
	Transit temperature
	Manufacturer
! USA	For US audiences only

1 Description

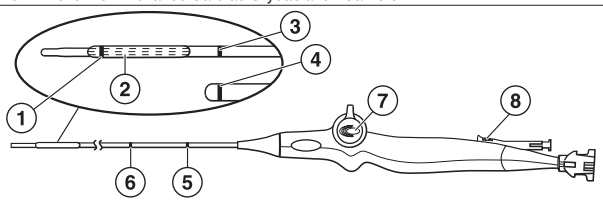
The Arctic Front Advance Cardiac Cryoablation Catheter (the catheter or the Arctic Front Advance Cryoballoon) is a flexible, over-the-wire balloon catheter used to ablate cardiac tissue. It is used together with a compatible Medtronic 12 Fr inner diameter sheath (the sheath), the CryoConsole, and related components. For device compatibility questions, contact Medtronic Technical Support.

The balloon reaches cryoablation temperatures when refrigerant is injected from the CryoConsole to the balloon segment. A thermocouple positioned inside the balloon provides temperature reading capability. The catheter is introduced into the vasculature by traditional, minimally invasive techniques.

There are two radiopaque markers on the catheter to confirm the position of the balloon using fluoroscopy. The proximal radiopaque marker is located approximately 10 mm (0.394 in) proximal to the balloon. The distal radiopaque marker is located at the end of the injection tube.

Note: The 12 Fr FlexCath sheath is compatible with the catheter. There is one radiopaque marker on the FlexCath sheath, located approximately 5 mm (0.197 in) proximal to the tip of the sheath (see *Figure 1*). When the catheter's proximal radiopaque marker and the FlexCath sheath's radiopaque marker are aligned, the balloon is approximately 5 mm (0.197 in) outside of the FlexCath sheath. There are two shaft markers on the proximal section of the catheter shaft to visually confirm the position of the balloon within the FlexCath sheath. When the distal marker on the shaft of the catheter is aligned with the handle of the FlexCath sheath, the balloon segment is located inside the FlexCath sheath. When the proximal marker on the shaft of the catheter is aligned with the handle of the FlexCath sheath, the balloon segment is outside the FlexCath sheath (see *Figure 1*).

Figure 1. Arctic Front Advance Cardiac Cryoablation Catheter



1 Distal catheter radiopaque marker
2 Deflated balloon segment
3 Proximal catheter radiopaque marker
4 FlexCath sheath radiopaque marker
5 Proximal catheter shaft marker
6 Distal catheter shaft marker
7 Deflection mechanism
8 Blue push button

The Arctic Front Advance Cardiac Cryoablation Catheter is available in 2 models, as described in the following table:

Model	Inflated balloon diameter
2AF234	23 mm (0.91 in)
2AF284	28 mm (1.10 in)

For details about the CryoConsole and how to use it with the catheter to perform cryoablation procedures, see the *CryoConsole Operator's Manual*.

1.1 Contents of package

The catheter is supplied sterile. The package contains the following items:

- 1 Arctic Front Advance Cardiac Cryoablation Catheter
- product documentation

2 Indications for use

The Arctic Front Advance Cardiac Cryoablation Catheter is indicated for the treatment of drug refractory recurrent symptomatic paroxysmal and persistent atrial fibrillation (episode duration less than 6 months).

3 Contraindications

The Arctic Front Advance Cardiac Cryoablation Catheter is contraindicated as follows:

- in the ventricle because of the danger of catheter entrapment in the chordae tendineae
- in patients with active systemic infections
- in conditions where the manipulation of the catheter within the heart would be unsafe (for example, intracardiac mural thrombus)
- in patients with cryoglobulinemia
- in patients with one or more pulmonary vein stents

4 Warnings and precautions

Anticoagulation therapy – Administer appropriate levels of peri-procedural anticoagulation therapy for patients undergoing left-sided and transseptal cardiac procedures. Administer anticoagulation therapy during and post-procedure according to the institution's standards. The Arctic Front Advance Cryoballoon was not studied for the safety of changes in anticoagulation therapy in patients with paroxysmal atrial fibrillation.

Balloon inflation or deflation – Do not inflate the balloon inside the sheath. Always verify with fluoroscopy or other appropriate visualization techniques that the balloon is fully outside the sheath before inflation to avoid catheter damage.

- Do not inflate the balloon while the catheter is positioned inside a pulmonary vein. Always inflate the balloon in the atrium and then position it at the pulmonary vein ostium. Inflating the balloon in the pulmonary vein may result in vascular injury.
- If the balloon cannot be inflated or deflated using the CryoConsole, have a Manual Retraction Kit on hand during the procedure. (Refer to the *CryoConsole Operator's Manual* for more detailed instructions on the Manual Retraction Kit).

Biohazard disposal – Discard all used catheters and sterile components in accordance with hospital procedures.

Cardioversion or defibrillation during ablation procedure – Disconnect the catheter's electrical connection before cardioversion or defibrillation. Failure to do so may trigger system messages indicating a need for catheter exchange.

Catheter handling – Use extreme care when manipulating the catheter. Lack of careful attention may result in injury such as perforation or tamponade.

- Do not use excessive force to advance, withdraw, or rotate the catheter, especially if resistance is encountered. Excessive force may lead to catheter damage, including kinking of the guide wire lumen within the balloon segment.
- Do not use the catheter if it is kinked, damaged, or cannot be straightened.
- Straighten the shaft before inserting or withdrawing the catheter.
- Do not at any time preshape or bend the catheter shaft or balloon segment. Bending or kinking the catheter shaft may damage internal structures and increase the risk of catheter failure. Prebending of the distal curve may damage the catheter.
- Catheter advancement should be performed using fluoroscopy or other appropriate techniques.
- Do not position the cryoballoon catheter within the tubular portion of the pulmonary vein to minimize phrenic nerve injury and pulmonary vein stenosis.

Catheter integrity – Do not use the catheter if it is kinked or damaged. If the catheter becomes kinked or damaged while in the patient, remove it and use a new catheter. Before injecting, the physician should ensure that there is no kink in the catheter.

Circular mapping catheter compatibility – Use only Medtronic circular mapping catheters compatible with the inner lumen of the Arctic Front Advance Cryoballoon. Use of another mapping catheter may damage the catheter or compromise the procedure.

Contrast media – Use appropriate levels of contrast media in patients with comorbidities such as recent history of renal disease. Follow contrast labeling and institutional procedures regarding the appropriate medical strategies to minimize risk when using contrast media.

Correct guide wire or circular mapping catheter insertion and positioning – Do not advance the balloon beyond the guide wire or circular mapping catheter to reduce the risk of tissue damage.

- Ensure that the guide wire or circular mapping catheter is inserted into the catheter and through the balloon portion for adequate support during vascular access insertion. Failure to do so may result in catheter damage.

Cryoablation near prosthetic heart valves – Do not pass the catheter through a prosthetic heart valve (mechanical or tissue). The catheter may become trapped in the valve, damaging the valve and causing valvular insufficiency or premature failure of the prosthetic valve.

Cryoadhesion – Do not pull on the balloon catheter, circular mapping catheter, sheath, umbilical cables, or CryoConsole while the balloon catheter or circular mapping catheter are frozen to tissue. This may lead to tissue injury. Before moving these components, use appropriate techniques to ensure that the balloon catheter and circular mapping catheter are not adhered to tissue.

Damage to lung or tracheobronchial tree – Damage to the lung or tracheobronchial tree has been observed in some subjects who have undergone left atrial ablation with the Arctic Front family. The physician should consider appropriate medical strategies to minimize the risk of damage to the lung or tracheobronchial tree.

Do not resterilize – Do not resterilize this device for the purpose of reuse. Resterilization may compromise the structural integrity of the device or create a risk of contamination from the device that could result in patient injury, illness, or death.

Embolism risk – Introducing any catheter into the circulatory system entails the risk of air or gas embolism, which may occlude vessels and lead to tissue infarction with serious consequences. Always advance and withdraw components slowly to minimize the vacuum created and therefore minimize the risk of air embolism.

Environmental limits – Perform cryoablation procedures only within the environmental parameters. Operating outside these parameters may prevent the start or completion of a cryoablation procedure. Refer to *Chapter 10, Specifications, page 33* for environmental parameters.

Esophageal injury – Esophageal ulcerations have been observed in some subjects who have undergone left atrial ablation with the Arctic Front family. As with other forms of left atrial ablation, the physician should consider appropriate medical strategies to minimize the risk of esophageal injury.

Fluid incursion – Do not expose the catheter handle or coaxial and electrical connectors to fluids or solvents. If these components get wet, the system may not function properly. This may lead to patient injury.

Fluoroscopy required for catheter placement – The use of fluoroscopy during catheter ablation procedures presents the potential for significant x-ray exposure to both patients and laboratory staff. Extensive exposure may result in acute radiation injury and increased risk for somatic and genetic effects. Only perform catheter ablation after giving adequate attention to the potential radiation exposure associated with the procedure, and taking steps to minimize this exposure. Give careful consideration before using the device in pregnant women.

For single use only – This device is intended only to be used once for a single patient. Do not reprocess or resterilize this device for the purpose of reuse. Reuse, reprocessing, or resterilization may compromise the structural integrity of the device or create a risk of contamination of the device that could result in patient injury, illness, or death.

Frequent flushing of the guide wire lumen – Flush the guide wire lumen before initial insertion and then frequently throughout the procedure to prevent coagulation of blood in the lumen. Flush the guide wire lumen with saline after each contrast injection.

Guide wire compatibility – Use only 0.081 cm (0.032 in) or 0.089 cm (0.035 in) guide wires with the catheter. Using another guide wire may damage the catheter or compromise the procedure.

Improper connection – Do not connect the cryoablation catheter to a radiofrequency (RF) generator or use it to deliver RF energy. This may cause catheter malfunction or patient injury.

Induced arrhythmias – Catheter procedures may mechanically induce arrhythmias.

Leakage current from connected devices – Use only isolated equipment (IEC 60601-1 Type CF equipment, or equivalent) with the CryoConsole and catheters or patient injury or death may occur.

Other catheters, devices, or wires – Avoid catheter entanglement with other catheters, devices, or wires. Such entanglement may necessitate surgical intervention.

Phrenic nerve impairment – To reduce the potential for phrenic nerve impairment, perform the following steps:

- Position the balloon as antral as possible and not in the tubular portion of the pulmonary vein. To ensure proper catheter position, observe the balloon shape and the balloon position within the anatomy.
- Monitor the status of the phrenic nerve continuously during right-sided pulmonary vein applications using an appropriate monitoring technique. One common monitoring technique is to continuously pace the phrenic nerve throughout each cryoablation application of the right pulmonary veins. While pacing, monitor diaphragm contraction by placing a hand on the abdomen to assess for loss of capture or changes in the strength of the diaphragmatic contraction.
- Stop ablation immediately if phrenic nerve impairment is observed.

Post-ablation period – Closely monitor patients undergoing cardiac ablation procedures during the post-ablation period for clinical adverse events.

Pressurized refrigerant – The catheter contains pressurized refrigerant during operation. Release of this gas into the circulatory system due to equipment failure or misuse may result in gas embolism.

Pulmonary vein narrowing or stenosis – Catheter ablation procedures inside or near pulmonary veins may induce pulmonary vein narrowing or stenosis. Do not ablate in the tubular portion of the pulmonary vein. The occurrence of this complication may necessitate percutaneous angioplasty or surgical intervention. Seven of 228 (3.1%) cryoablated study subjects had one or more stenosed pulmonary veins (PVs) detected during study imaging. (See *Section 5.8* for study results.)

Qualified users – This cryoablation system should be used only by or under the supervision of physicians trained in cryoablation procedures.

Required use environment – Cryoablation procedures should be performed only in a fully equipped facility.

RF ablation – Before powering up an RF generator or applying RF energy, disconnect the cryoablation catheter from the CryoConsole to avoid an error message and unnecessary catheter replacement.

Septal damage – Always deflate the balloon and withdraw the balloon into the transseptal sheath before removing the balloon from the left atrium. Crossing the septum while the balloon is unsheathed, inflated, or inflating in the septal puncture site may cause serious septal damage.

Steerable sheath compatibility – Use only a compatible Medtronic12 Fr inner diameter sheath with the Arctic Front Advance Cryoballoon. Using another sheath may damage the catheter or balloon segment.

Sterile package inspection – Inspect the sterile packaging and catheter before use. If the sterile packaging or catheter is damaged, do not use the catheter. Contact your Medtronic representative.

System compatibility – Use only Medtronic cryoablation catheters, refrigerant tanks, and components with the CryoConsole. The safety and use of other catheters or components has not been tested.

5 Clinical summary

Study title:	STOP-AF: A Randomized, Controlled Clinical Trial of Catheter Cryoablation in the Treatment of Paroxysmal Atrial Fibrillation
Number of centers:	26 centers in the United States and Canada
Number of subjects:	245 randomized subjects

5.1 Study purpose

To evaluate the safety and effectiveness of the Arctic Front Cardiac Cryoablation Catheter System, including the FlexCath Steerable Sheath, Freezor MAX Cardiac Cryoablation Catheter, and CryoConsole (Gen V) in adult patients with paroxysmal atrial fibrillation who have failed one or more Atrial Fibrillation drugs.

5.2 Study scope, design and methods

The study was a prospective, randomized, controlled, multicenter, pivotal clinical investigation conducted at 26 investigational sites (23 in the United States and 3 in Canada). Subjects with paroxysmal atrial fibrillation (PAF) referred for ablative intervention after efficacy failure of one or more Study Atrial Fibrillation (AF) Drugs (flecainide, propafenone, or sotalol) (Amiodarone was not considered a study AF Drug) were randomized 2:1 to cryoablation intervention (Experimental Subjects, ES) or to a Study AF Drug (Control Subjects, CS). Subjects were followed for 12 months with scheduled and symptom-driven assessments to detect recurrent atrial fibrillation by means of periodic electrocardiograms, weekly scheduled trans-telephonic monitoring, patient-initiated trans-telephonic monitoring, and 24-hour Holter monitoring at 6 and 12 months. The first 90 days after study therapy was initiated was considered a blanked period for all subjects.

5.3 Study endpoints

The primary effectiveness outcome was Treatment Success, defined on the basis of Chronic Treatment Failure events and the occurrence of Acute Procedural Success.

- **Treatment Success:** (TS), defined for CS as freedom from any Chronic Treatment Failure events, and for ES as both Acute Procedural Success **and** freedom from Chronic Treatment Failure from Day 0 through the 12 month follow-up visit. This comparison of proportions was to be performed using a 2-sided Fisher's Exact Test of binomial proportions with a = 0.05 and b = 0.20, with an estimate of TS in the groups of 40% Control and 60% Experimental and a 2:1 randomization, giving a sample size calculation of 240 evaluable subjects.
  - **Acute Procedural Success:** (APS), defined as the electrical isolation of ≥ 3 pulmonary veins from the left atrium (as reported after the first procedure) was an additional primary effectiveness outcome measure, for ES only.
  - **Chronic Treatment Failure:** (CTF), defined as Detectable AF (during the Non Blanked Follow-up Period), the use of Non Study AF Drugs, or an AF Intervention (Day 0 through the 12 month follow-up).

The initial cryoablation treatment date or the first day of AF Drug therapy was considered the Start Date for all subjects. Subjects were then followed for 12 months from their Start Date with scheduled and symptom-driven assessments to detect recurrent AF (Detectable AF) by means of periodic electrocardiograms (ECG), weekly scheduled transtelephonic monitoring (TTM), subject-initiated TTMs, and 24-hour Holter monitoring at 6- and 12- months. The 90 day interval following the Start Date was considered a Blanked Follow-up Period for all subjects. It was during this time period that the Control Subjects underwent AF Drug optimization and that Experimental Subjects were allowed one repeat cryoablation as needed. Occurrences of AF during the Blanked Follow-up Period were not considered as Chronic Treatment Failure (CTF) and did not count as an event against the primary objective. Control Subjects were allowed one crossover cryoablation treatment only after they demonstrated CTF. All repeat and crossover cryoablations required review and approval by the Medical Monitor or Principal Investigator.

The primary safety outcomes were Cryoablation Procedure Events and Major Atrial Fibrillation Events.

- **Cryoablation Procedure Events:** (CPE) defined for ES **only** as specifically categorized device- or procedure-related serious adverse events (SAE) with onset within 7 days of cryoablation (access site complications, cardiac damage, embolic complications, arrhythmias, persistent phrenic nerve palsy, or death) or with onset at any time through 12 months of follow-up (pulmonary vein stenosis or atrio-esophageal fistula). (*Table 1*)

Table 1. Cryoablation Procedure Event Categories

Cryoablation Procedure Events (CPE)	With onset between Day 0 and:
Access site complications requiring • Transfusion of 3 or more units; or • Surgical intervention; or • Permanent loss of functional impairment	Day 7
Cardiac damage (including MI)	Day 7
• Pulmonary vein stenosis	12-month follow-up visit[a]
• Atrio-esophageal fistula	12-month follow-up visit[a]
Embolic complications (including stroke)	Day 7
Arrhythmias	Day 7
Persistent phrenic nerve palsy	Day 7
Death	Day 7

[a] This CPE will be assessed through the completion of within window study follow-up.

- **Major Atrial Fibrillation Events:** (MAFE) defined for CS and ES as serious adverse events in the categories of cardiovascular death, myocardial infarction, stroke, or any hospitalization primarily related to AF recurrence/ablation, atrial flutter ablation (excluding Type I), systemic embolization, congestive heart failure, hemorrhagic event or anti-arrhythmic drug initiation, adjustment or complication. (*Table 2*)

Table 2. Major Atrial Fibrillation Events Categories

Major Atrial Fibrillation Events (MAFE)
Cardiovascular death
Myocardial infarction (MI)
Stroke
Associated with or leading to a hospitalization for (primary reason): • AF recurrence or ablation • Atrial flutter ablation (excluding Type I) • Systemic embolization (not stroke) • Congestive heart failure • Hemorrhagic event (not stroke) • Anti-arrhythmic drug initiation, adjustment, or complication

5.4 Subject accountability

Enrollment and accountability are summarized in the following table.

Table 3. Subjects accountability and disposition

Subject disposition	Control subjects	Experimental subjects	All subjects
Subjects provisionally enrolled and randomized	87	171	258
Screen failures	1	5	6
Withdrawal of consent	4	3	7
Subjects enrolled	82	163	245
Death	0	1	1
Lost to follow-up	0	0	0
Withdrawal of consent	3	0	3
Subjects completing 12 month follow-up	79	162	241
Control subjects crossing over to cryoablation	65	----	----
Experimental subjects undergoing reablation	----	31	----

Study populations for analysis were:

- Safety Population (n = 245): pre-specified, included **all** subjects (82 CS, 163 ES) who were enrolled, randomized, and received treatment.
- Effectiveness Populations
  - Modified intent-to-treat (n = 245): pre-specified included **all** subjects (82 CS, 163 ES) who were enrolled, randomized, and received treatment.
  - Per protocol Population (n = 181): pre-specified, included those subjects that received treatment in their randomized group and completed the Blanked Follow-up Period, having complete assessments for detection of AF through 12 months of follow-up including at least 80% compliance with rhythm monitoring, and having the absence of any major protocol violations.
- Cryoablated Control Population (n = 65): pre-specified, included those CS who underwent crossover cryoablation. Control subjects were allowed to undergo one cryoablation procedure under the protocol. All control subject crossovers were required to be approved by the Principal Investigator or Medical Monitor. Cryoablated control subjects were followed for 12 months from the date of the cryoablation procedure.
- Reablated Experimental Population (n = 31): pre-specified, included ES who underwent repeat cryoablation during the Blanked Follow-up Period. Experimental subjects were allowed to undergo an additional cryoablation procedure during the 90 day blanking period. Reablated experimental subjects maintained the same follow-up schedule as determined by initial study cryoablation procedure.

5.5 Subject demographics

The STOP AF study population consisted of mostly white ethnic background (94.3%), had a mean age of 56.6 years with 77.1% being male. The baseline characteristics were comparable between the randomized groups, as summarized in *Table 4* and *Table 5*.

Table 4. Baseline demographics - age, echocardiography, AF symptoms, SF-36 score

	All subjects mean (SE) N median (min, max) N = 245	Control subjects mean (SE) N median (min, max) N = 82	Experimental subjects mean (SE) N median (min, max) N = 163	Difference [95% 95%C][a]	p value
Age (years)	56.6 (0.60) 245 57.0 (26, 75)	56.4 (1.04) 82 56.5 (26, 72)	56.7 (0.73) 163 58.0 (33, 75)	0.3 [–2.2, 2.8]	0.797
Left atrial AP diameter (mm)	40.5 (5.4) 245 40 (24, 54)	40.9 (6.0) 82 40.5 (28, 54)	40.3 (5.1) 163 40 (24, 50)	–0.7 [–2.1, -0.8]	0.353
Left ventricular EF (%)	60.2 (5.6) 244 60 (40, 76)	60.7 (6.4) 82 60 (45, 76)	60.0 (5.7) 162 60 (40, 75)	–0.7 [–2.3, -0.9]	0.407
Symptomatic AF in the 2 months prior to enrollment	23.2 (2.54) 239 10.0 (2, 300)	21.2 (3.63) 80 10.0 (2, 250)	24.3 (3.36) 159 10.0 (2, 300)	3.0 [–7.6, 13.7]	0.540
Overall SF-36 score	70.63 (1.115) 231 74.0 (15.0, 98.0)	70.37 (1.716) 78 74.50 (29.0, 98.0)	70.76 (1.442) 153 74.00 (15.0, 98.0)	0.4% [–4.3, 5.0%]	0.870

[a] AP = Antero-posterior; EF = Ejection Fraction

Table 5. Baseline demographics - gender, ethnicity and NYHA Class

		All subjects % (n) N = 245	Control subjects % (n) N = 82	Experimental subjects % (n) N = 163	p value
Gender	Male	77.1% (189)	78.0% (64)	76.7% (125)	0.873
	Female	22.9% (56)	22.0% (18)	23.3% (38)	
Ethnicity	White	94.3% (231)	92.7% (76)	95.1% (155)	0.696
	Black	1.2% (3)	2.4% (2)	0.6% (1)	
	Hispanic	0.8% (2)	1.2% (1)	0.6% (1)	
	Asian	1.6% (4)	1.2% (1)	1.8% (3)	
	Other	2.0% (5)	2.4% (2)	1.8% (3)	
NYHA[a] Class	None / Class I	93.5% (229)	93.9% (77)	93.3% (152)	1.000
	Class II	6.5% (16)	6.1% (5)	6.7% (11)	
Cardiovascular risk factors	Diabetes	7.3% (18)	8.5% (7)	6.7% (11)	0.612
	Hypertension	42.4% (104)	45.1% (37)	41.1% (67)	0.585
	Dyslipidemia	48.2% (118)	48.8% (40)	47.9% (78)	0.893

[a] NYHA = New York Heart Association

Previously failed AF Drugs for efficacy were comparable between study groups with 36% of all study subjects having failed flecainide, 47% having failed propafenone, and 29% having failed sotalol.

5.6 Results

Procedural data

The Arctic Front Cryocatheter parameters for first procedures in ES (n = 163) included approximately 3 cryoapplications for each of the 4 major pulmonary veins at a mean intra-catheter temperature between -48.6 and -54.1°C, with a median duration of 240 s per cryoapplication (*Table 6*).

Table 6. Arctic Front Cryocatheter Cryoapplication Parameters by Pulmonary Vein Location, First Experimental Procedures (N = 163)

Cryoapplication parameters	RSPV[a] mean (SE) N median (min, max)	RIPV[a] mean (SE) N median (min, max)	LSPV[a] mean (SE) N median (min, max)	LIPV[a] mean (SE) N median (min, max)
# of cryo apps	2.9 (0.12) 161	2.8 (0.14) 154	3.6 (0.14) 150	3.2 (0.11) 152

Table 6. Arctic Front Cryocatheter Cryoapplication Parameters by Pulmonary Vein Location, First Experimental Procedures (N = 163) (continued)

Cryoapplication parameters	RSPV[a] mean (SE) N median (min, max)	RIPV[a] mean (SE) N median (min, max)	LSPV[a] mean (SE) N median (min, max)	LIPV[a] mean (SE) N median (min, max)
	3.0 (1, 11)	2.0 (0, 11)	3.0 (1, 12)	3.0 (1, 9)
Measured temp (°C)	–50.70 (0.73) 460 –51.0 (–80.0, 33.0)	–48.63 (1.00) 405 –48.0 (–81.0, 35.0)	–54.12 (0.79) 508 –55.0 (–81.0, 36.0)	–50.78 (0.78) 484 –49.0 (–81.0, 33.0)
Duration (secs)	196.9 (3.54) 473 240.0 (3, 240)	205.4 (3.69) 428 240.0 (3, 240)	219.3 (2.80) 534 240.0 (1, 240)	230.1 (2.07) 488 240.0 (4, 360)

[a] PV = pulmonary vein, R = right, L = left, I = inferior, S = superior.

The Freezor MAX Cryocatheter was used for gap cryoablations in a small proportion of major pulmonary veins during first experimental procedures (initial study cryoablation procedure). (*Table 7*)

Table 7. Freezor MAX Cryocatheter Use by Pulmonary Vein Location, First experimental procedures (N = 163)

Freezor MAX Cryocatheter Use	RSPV[a]% (n)	RIPV[a]% (n)	LSPV[a]% (n)	LIPV[a]% (n)
Experimental first procedures	4.9% (8)	9.2% (15)	4.3% (7)	4.3% (7)

[a] PV = pulmonary vein, R = right, L = left, I = inferior, S = superior.

The first experimental procedure lasted a mean of 371 min, with investigational devices inserted in the subject vasculature for a mean of 181 min. Cryoablation time averaged 65.7 min, and total fluoroscopy time averaged 62.8 min (*Table 8*).

Table 8. Cryoablation procedural durations, First experimental procedures (N = 163)

Procedure, Cryocatheter & fluoroscopy times	Total procedure duration mean (SE) N median (min, max)	Cryocatheter insertion time mean (SE) N median (min, max)	Total ablation time mean (SE) N median (min, max)	Total fluoroscopy time mean (SE) N median (min, max)
Experimental first procedures (min)	371.4 (7.89) 163 349.0 (200.0, 650.0)	181.2 (5.86) 162 169.0 (72.0, 427.0)	65.7 (2.70) 162 56.8 (17.0, 179.8)	62.8 (2.55) 162 54.0 (8.0, 229.0)

Compliance with follow-up and rhythm monitoring requirements

Follow-up compliance with key assessments was high, exceeding 90% in all cases except for Holter compliance which was as low as 72% at the 6 month follow-up visit in the Control group. The Holter monitoring assessment protocol requirements for cryoablated control subjects was reduced because cryoablated control subjects were considered chronic treatment failures. This meant further Holter monitoring was not required.

Pulmonary vein CT/MRI imaging was performed prior to a subjects first cryoablation procedure (Experimental and Cryoablated Control) as well as at 6 and 12 months post-cryoablation procedure for pulmonary vein stenosis surveillance (*Table 9*).

Effectiveness outcomes and measures

Table 9. Compliance with follow-up and monitoring requirements

Parameter		Control subjects %[a]	Experimental subjects %[b]	All subjects %[c]
Office visits	3 months	98.8%	100.0%	99.6%
	6 months	97.6%	100.0%	99.2%
	12 months	96.3%	99.4%	98.4%
Weekly TTMs		91.5%	91.5%	91.5%
Scheduled TTMs[d]		3,841	7,983	11,824
Unscheduled TTMs[d]		3,016	2,084	5,100
24° h Holter monitors	6 months[e]	72.8%	85.9%	81.6%
	12 months[f]	74.7%	88.9%	84.2%
Imaging of pulmonary veins	Baseline	100%	100%	100%
	6 months	95.4%	96.9%	96.5%
	12 months	93.8%	97.5%	96.4%

[a] Denominator = 82 except for imaging of pulmonary veins for which denominator = 65 cryoablated Control Subjects eligible for 6 month study and 47 eligible for 12 month study at time of report.

[b] Denominator = 163 Experimental Subjects.

[c] Denominator = 245 except for imaging of pulmonary veins for which denominator = 228 cryoablated subjects eligible for 6 month study and 205 eligible for 12 month study at time of report.

[d] Number of TTM recordings

[e] Has a holter recording between 150 and 210 days

[f] Has a holter recording between 335 and 395 days

The STOP AF trial defined three (3) Primary Effectiveness Outcome Measures:

- **Acute Procedural Success (APS)**, the electrical isolation of ≥ 3 pulmonary veins from the left atrium as reported after the first procedure (ES).
- **Chronic Treatment Failure (CTF)**, defined as Detectable AF during the Non Blanked Follow-up Period, or use of Non Study AF Drugs, or an AF Intervention through the 12 month follow-up visit. The protocol stipulated that subjects could not be counted as a CTF for Detectable AF during the 90 day blanking period. However, subjects could have a CTF for use of Non Study AF Drugs or AF Intervention during the 90 day blanking period.
- **Treatment Success (TS)**, defined as:
  - **Experimental Subjects:** Acute Procedural Success and Freedom from Chronic Treatment Failure.
  - **Control Subjects:** Freedom from Chronic Treatment Failure.

Acute Procedural Success: Acute Procedural Success was achieved in 98.2% of ES. Electrical isolation was achieved in >95% of each of the 4 main pulmonary veins attempted. Electrical isolation was assessed by pacing to determine electrical conduction between the pulmonary vein and left atrium had been interrupted, by evidence of entrance and, where assessable, exit block (*Table 10*).

Table 10. Experimental First Procedures: Acute Pulmonary Vein Isolation rates

Vein(s)	Proportion isolated % (n / N)
≥ 3 PVs (APS[a])	98.2% (160 / 163)
RSPV[b]	98.1% (159 / 163)
RIPV[b]	97.4% (152 / 156)
LSPV[b]	96.7% (146 / 151)
LIPV[b]	97.4% (149 / 153)

[a] APS = Acute Procedural Success

[b] PV = pulmonary vein, R = right, L = left, I = inferior, S = superior

Treatment Success: The Primary Effectiveness Outcome, Treatment Success, was observed in 69.9% of ES and 7.3% of CS (difference 62.6%, p < 0.001). (See *Figure 2* and *Table 11*).

Figure 2. Kaplan Meier Display of Continued Treatment Success by Group Through 12 months, Modified Intent to Treat Population

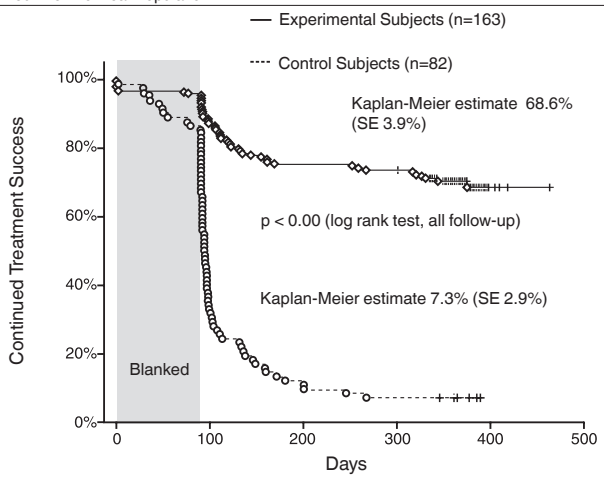


Table 11. Primary effectiveness outcome: Treatment success (mITT Population)

Primary effectiveness outcome	Control subjects % (n / N) [95% CI]	Experimental subjects % (n / N) [95% CI]	Difference [95% CI]	p value
Treatment success	7.3% (6 / 82) [2.7, 15.2%]	69.9% (114 / 163) [62.3, 76.9%]	62.6% [53.6, 71.6%]	<0.001

Additional Measures of Effectiveness: Other relevant measures confirmed treatment effectiveness for PAF:

- **AF Drug Free Treatment Success:** Of the 114 ES with Treatment Success, 101 (62.0%) were Treatment Successes without the use of any AF Drugs at any time during the Non Blanked Follow-up Period.
  - 62.0% (101/163) of experimental subjects were off AF drugs during the entire non-blanked follow-up period, while 8% (13/163) of the experimental subjects that were considered treatment successes were treated with a previously failed AF drug during the non-blanked follow-up period (*Table 11*).

Table 12. Treatment Success and Atrial Fibrillation Drug Therapy

AF Drug Status during Non-Blanked Follow-up Period	Control Subjects % (n / N) [95% CI] N = 82	Experimental Subjects % (n / N) [95% CI] N = 163
Treatment Success	7.3% (6 / 82) [2.7, 15.3%]	69.9% (114 / 163) [62.3, 76.9%]
Treatment Success Without Any AF Drugs	0.0% (0 / 82) [0.0, 4.4%]	62.0% (101 / 163) [54.0, 69.4%]
Treatment Success With Any AF Drugs	7.3% (6 / 82) [2.7, 15.3%]	8.0% (13 / 163) [4.3, 13.3%]

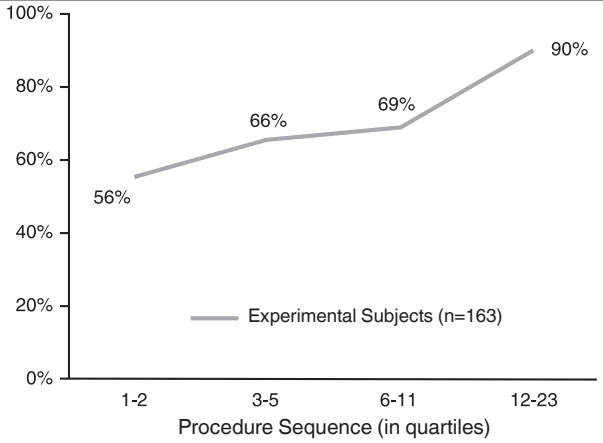
- **Reduced Use of AF Drugs:** 74% of all ES were off AF Drugs during the last 3 months of follow-up, and 87% of ES with Treatment Success were free from any AF Drug use during the last 3 months of follow-up.
- **Improved Quality of Life:** ES showed significantly improved SF-36 quality of life score through 12 months of follow-up in every subscale.
- **Reduced Symptoms:** ES had a significant reduction in AF symptomatic burden after cryoablation. At baseline 100% of patients had symptoms, at 12 months only 20% had symptoms from PAF.
- **Effectiveness by Balloon Size**: Treatment success was 70% among cryoablations with balloon size 23 mm, 63.3% among cryoablations with balloon size 28 mm, and 76.2% among subjects with both balloon sizes utilized (*Table 12*).

Table 13. Primary Effectiveness Outcome; Proportion of ES with Treatment Success at the 12 Month Follow-up Visit

Cohort	Experimental Subjects % (n / N) [95% CI] N = 163
Treatment success	69.9% (114 / 163) [62.3, 76.9%]
By balloon size:	
Balloon size 23 only	70% (35 / 50) [55.4, 82.1%]
Balloon size 28 only	63.3% (31 / 49) [48.3, 76.6%]
Both balloon sizes	76.2% (48 / 63) [63.8, 86.0%]

- **Effectiveness by number of procedures performed**: A post-hoc analysis revealed that procedure sequence had an impact on treatment success in the STOP AF trial. *Figure 3* illustrates that treatment success improved as the number of procedures performed increased at a given site (see *Table 12* and *Figure 3*).

Figure 3. Procedure Frequency and Treatment Success



Atrial Flutter: Adjunctive cryoablation of the cavo-tricuspid isthmus (CTI) was performed in 66 ES.Bidirectional block was achieved in 97.0% of these subjects at the first attempt. Freedom from Flutter Chronic Treatment Failure (Flutter CTF) was observed in 70.7% (29 / 41) of those subjects with a history of atrial flutter at baseline and 84.0% (21 / 25) of those subjects with no history of atrial flutter at baseline.

5.7 Safety outcomes and measures

Serious Adverse Events were defined as any undesirable clinical occurrence in a study subject that included any of the following events:

- Any adverse event resulting in death
- Any adverse event, which is life-threatening
- Any adverse event resulting in inpatient hospitalization > 48 hours or prolongation of existing hospitalization by two or more days
- Any adverse event resulting in a persistent, significant disability or incapacity
- Any adverse event resulting in a congenital anomaly or birth defect

Primary Safety Outcome Measures were defined as:

- **Cryoablation Procedure Events** (CPEs), assessed only for ES for procedural safety, which were device or procedure-related serious adverse events (SAE) categorized as access site complications, cardiac damage, PV stenosis, embolic complications, arrhythmias, unresolved phrenic nerve palsy, and death; and
- **Major Atrial Fibrillation Events** (MAFEs), which were serious adverse events categorized as cardiovascular death, myocardial infarction, stroke, or hospitalization for AF. Overall disease and treatment morbidity, exclusive of the experimental cryoablation procedure, was assessed for both the control and experimental treatment subjects by this measure.

Primary Safety Outcomes (two were defined by the STOP AF Study Protocol):

- The proportion of experimental group safety subjects with one or more CPEs.
- The proportion of safety subjects in either group free of MAFEs at the 12 month follow-up visit.

Both safety outcomes met pre-specified criteria and success was achieved for the safety evaluation.

Cryoablation Procedure Events: Data for subjects who were randomized to the experimental therapy and received treatment are included in the analysis of CPE shown in the following table. ES had a 3.1% (6.3% UCB) rate of CPE compared to a pre-specified UCB of 14.8% ($p < 0.001$). Observed CPEs included 2 instances of cardiac damage (one peri-procedural MI, one perforation with tamponade), one arrhythmia, and two cases of pulmonary vein stenosis (*Table 14*).

Table 14. Primary safety outcome: Cryoablation procedure events

Primary safety outcome: CPE	Experimental subjects % (n / N)	95% upper confidence bound	p value
Experimental subjects with one or more CPE	3.1% (5 / 163)	6.3%	<0.001

Table 15 lists the individual CPEs that were reported during the STOP AF trial.

Table 15. Experimental Subjects; Cryoablation Procedure Event Categories

CPE Categories	Experimental Subjects% (n) N = 163	95% One-Sided Upper Confidence Bound[a]
Access site complications	0.0% (0)	1.8%
Cardiac damage (including myocardial infarction)	1.2% (2)	3.8%
Embolic phenomena (including stroke)	0.0% (0)	1.8%
Arrhythmias	0.6% (1)	2.9%
Persistent phrenic nerve injury[b]	0.0% (0)	1.8%
Death	0.0% (0)	1.8%
Pulmonary vein stenosis[c]	1.2% (2)	3.8%

[a] Based on Clopper-Pearson confidence intervals

[b] Four (4) Experimental subjects had phrenic nerve injury persisting at 12-months of follow-up; none were adjudicated as SAE. They were not included as a CPE because they were not adjudicated as an SAE.

[c] Five (5) Experimental Subjects had one or more pulmonary veins with stenosis during study follow-up; 2 of these adverse events were adjudicated as SAE.

Pulmonary Vein Stenosis: The PV stenosis rate was 3.1% (5/163) in ES and 3.1% (7/228) for all subjects having undergone cryoablation (*Table 16*). Stenosis was defined in the protocol as a reduction in the calculated pulmonary vein cross sectional area to <25% of the baseline pulmonary vein cross sectional area. Five (5) subjects had radiologic findings only, without symptoms of any kind. Two (2) subjects experienced significant symptoms and disability (i.e. Serious Adverse Event) and therefore these two pulmonary vein stenosis events were adjudicated as a CPE.

Table 16. Occurrence of Pulmonary Vein Stenosis in Cryoablated Subjects

Proportion of Subjects	Experimental			Control	All Subjects
	One Cryoablation[a] % (n) [95% CI][b]	Two Cryoablations (n) [95% CI][b]	Any Cryoablation % (n) [95% CI][b]	One Cryoablation (n) [95% CI][b]	Any Cryoablation (n) [95% CI][b]

Table 16. Occurrence of Pulmonary Vein Stenosis in Cryoablated Subjects (continued)

Proportion of Subjects	Experimental			Control	All Subjects
	N = 132	N = 31	N = 163	N = 65	N = 228
Stenosis in ≥1 PV at 6 or 12 Months[c]	2.3% (3) [0.5, 6.5%]	6.5% (2) [0.8, 21.4%]	3.1% (5) [1.0, 7.0%]	3.1% (2) [0.4, 10.7%]	3.1% (7) [1.2, 6.2%]

[a] One ES also had RF ablation for atrial fibrillation 72 days after the initial cryoablation.

[b] Clopper-Person confidence intervals.

[c] Each subject is counted only once within each time point.

CI = confidence interval, PV = pulmonary vein.

Phrenic Nerve Palsy: Twenty-nine (29) occurrences of Phrenic Nerve Palsy (PNP) in 28 subjects were reported (*Table 17*). Overall, 11.2% (29 / 259) of all cryoablation procedures were associated with PNP. Twenty-five (25) (11%) were associated with PNP, which resolved within 12 months of follow-up, and 4 (1.8%) were associated with persistent PNP (*Table 18*). Fifteen (15) subjects were asymptomatic, 13 had one or more associated symptoms including dyspnea on exertion (6), dyspnea (5), shortness of breath (2), orthopnea (2) and cough (1) during the period in which hemi-diaphragmatic abnormalities were noted. One occurrence of PNP was adjudicated as an SAE.

Table 17. Phrenic Nerve Palsy; Procedures

Phrenic Nerve Palsy	First Experimental Ablation Subjects % (n) [95% CI] N = 163[a]	Experimental Reablation Subjects % (n) [95% CI] N = 31[a]	Crossover Control Ablation Subjects % (n) [95% CI] N = 65[a]	All Ablated Subjects % (n) [95% CI] N = 228[a]
Procedures free of PNP[b]	87.7% (143) [81.7, 92.3%]	90.3% (28) [74.2, 98.0%]	90.8% (59) [81.0, 96.5%]	88.8% (230) [84.3, 92.4%]
Procedures associated with PNP[b]	12.3% (20) [7.7, 18.3%]	9.7% (3) [2.0, 25.8%]	9.2% (6) [3.5, 19.0%]	11.2% (29) [7.6, 15.7%]

[a] N = the total number of subjects undergoing cryoablation procedures of this type.

[b] One subject had 2 events of PNP, one with the first experimental cryoablation and one with the second, reablation procedure (both of which resolved).

Table 18. Phrenic Nerve Palsy; Subjects

Phrenic Nerve Palsy	First Experimental Ablation Procedures % (n) [95% CI] N = 163[a]	Experimental Reablation Procedures % (n) [95% CI] N = 31[a]	Crossover Control Ablation Procedures % (n) [95% CI] N = 65[a]	All Ablation Procedures % (n) [95% CI] N = 259[a]
All Subjects with PNP	12.3% (20) [7.6, 18.3%]	9.7% (3) [2.0, 25.8%]	9.2% (6) [3.5, 19.0%]	12.3% (28) [8.3, 17.3%]
Persistent PNP (radiographic)	2.5% (4) [0.7, 6.2%]	0.0% (0) [0.0, 11.2%]	0.0% (0) [0.0, 5.5%]	1.8% (4) [0.5, 4.4%]
Resolved PNP (radiographic)	9.8% (16) [5.7, 15.5%]	9.7% (3) [2.0, 25.8%]	9.2% (6) [3.5, 19.0%]	11.0% (25) [7.2, 15.8%]

[a] N = the total number of cryoablation procedures of this type.

Major Atrial Fibrillation Events: Data for subjects who were randomized to either experimental or drug treatment, received such treatment and were followed through 12 months post treatment start are included in the analysis for MAFE shown in the following table. The analysis was an evaluation of non-inferiority of MAFE rates in ES compared to Control. The clinically significant difference (δ) for establishing noninferiority for the MAFE free rate was set at 10% ES had a 96.9% Freedom from MAFE rate, compared to CS who had a 91.5% rate ($p < 0.0001$, non-inferiority for difference ≤ 10%) (see *Table 19*).

Table 19. Primary safety outcome: Freedom from MAFE

Primary safety outcome: Freedom from MAFE	Control subjects % (n /N) [95% CI]	Experimental subjects % (n / N) [95% CI]	Difference [95% CI]	Test for non-inferiority d = 0.10 p value
Freedom from MAFE (through 12 month follow-up)	91.5% (75 / 82) [83.2, 96.5%]	96.9% (158 / 163) [93.0, 99.0%]	5.4% [–1.1, 12.1%]	<0.001

The observed categories of MAFEs are displayed for both treatment groups below (*Table 20*).

Table 20. Subjects with one or more MAFEs by category, safety population

MAFE Categories	Control subjects% (n / N) [95% CI]	Experimental subjects % (n / N) [95% 95% CI]	Difference [95% CI]	p value
Any MAFE	8.5% (7 / 82) [3.5, 16.8%]	3.1% (5 / 163) [1.0, 7.0%]	–5.4% [–12.1, 1.1%]	0.112
Cardiovascular death	0.0% (0 / 82) [0.0, 4.4%]	0.6% (1 / 163) [0.0, 3.4%]	0.6% [–0.6, 1.8%]	1.000
Hospitalization for:	7.3% (6 / 82) [2.7, 15.2%]	1.8% (3 / 163) [0.4, 5.3%]	–6.5% [11.5, 0.5%]	0.064
AF recurrence or ablation	6.1% (5 / 82) [2.0, 13.7%]	0.6% (1 / 163) [0.0, 3.4%]	–5.5% [–10.8, –0.2%]	0.017
Atrial flutter ablation (excluding Type I)	1.2% (1 / 82) [0.0, 6.6%]	0.0% (0 / 163) [0.0, 2.2%]	–1.2% [–3.6, 1.2%]	0.335
Systemic embolization (not stroke)	0.0% (0 / 82) [0.0, 4.4%]	0.0% (0 / 163) [0.0, 2.2%]	NA	NA
Congestive heart failure	0.0% (0 / 82) [0.0, 4.4%]	1.2% (2 / 163) [0.1, 3.4%]	–1.2% [–5.0, 2.5%]	1.000
Hemorrhagic event (not stroke)	2.4% (2 / 82) [0.3, 8.5%]	1.2% (2 / 163) [0.1, 4.4%]	–1.2% [–5.0, 2.5%]	0.603
Anti-arrhythmic drug: initiation, adjustment, or complication[a]	4.9% (4 / 82) [1.3, 12.0%]	0.6% (1 / 163) [0.0, 3.4%]	–4.3% [–9.1, 0.5%]	0.044
Myocardial infarction	0.0% (0 / 82) [0.0, 4.4%]	0.6% (1 / 163) [0.0, 3.4%]	0.6% [–0.6, 1.8%]	1.000
Stroke	0.0% (0 / 82) [0.0, 4.4%]	0.6% (1 / 163) [0.0, 3.4%]	0.6% [–0.6, 1.8%]	1.000

[a] Excludes control subject treatment initiation

As described in *Table 21*, only 1 ES had a MAFE categorized as stroke. There was an additional 4 (3 ES and 1 CS) strokes reported during the 12 month follow-up. All 4 subjects had recovered completely at the time of the 12 month follow-up. *Table 21* provides additional detail for the 5 strokes that were reported during the 12 month follow-up (1 MAFE stroke, 4 non-MAFE stroke).

Table 21. Subjects with Stroke During Study Follow-up

Group	Diagnosis (verbatim)	Onset	Ablation Related[a]	Clinical Outcome	Event Severity	SAE
Exp	Small hemorrhagic stroke	Day 183	No	Recovered completely	Mild	No
Exp	Lacunar infarct	Day 51	Unknown[b]	Recovered completely	Mild	No
Cont	Stroke	Same day as X-over ablation	Yes	Recovered completely	Severe	No
Exp	"Sees white spots in both eyes"	~1 month after cryoablation	No	Recovered completely	Mild	No
Exp	Subarachnoid hemorrhage	Day 260	No	Recovered completely	Severe	Yes

[a] Ablation-related = procedure-related or device-related adverse event.

[b] Age of infarct indeterminate when discovered and could not be temporally linked to procedure or device. Adjudicated as of unknown relatedness

Exp = Experimental, Cont = Control, X-over = crossover

5.8 Additional safety information from the STOP AF Pivotal Trial

Serious adverse events (SAE)

A total of 55 serious adverse events (SAE) in 32 study subjects were reported by Investigators during the first 12 months of study follow-up (See *Table 22*). Twenty-two (22) SAE occurred in 12 CS (12 MAFE and 10 other SAE) (See *Table 23*) and 33 SAE occurred in 20 ES (5 CPE, 8 MAFE and 20 other SAE) (See *Table 22*). The overall proportion of CS with one or more SAE was 14.6% and for ES was 12.3%, a slightly lower rate of SAE occurrence that was not significantly different (p = 0.688).

Table 22. Subjects with one or more serious adverse events, safety population

Serious adverse events	Control subjects % (n /N)	Experimental subjects % (n / N)	Difference [95% CI]	p value
Serious adverse events	14.6% (12 / 82)	12.3% (20 / 163)	-2.3% [–11.5, 6.8%]	0.688

The SAE occurring in CS and ES are listed in the following tables (*Table 23* and *Table 22*).

Table 23. Serious adverse events occurring in control subjects, safety population

Serious Adverse Events	Control Subjects % (n / n) N=82
Atrial Fibrillation	4.9% (4/82)
Atrial Flutter	2.4% (2/82)
Appendicitis	1.2% (1/82)
Atrial Thrombosis	1.2% (1/82)
Cardiac Tamponade	1.2% (1/82)
Cardio Respiratory Arrest	1.2% (1/82)
Gastrointestinal Hemorrhage	1.2% (1/82)
Injection Site Infection	1.2% (1/82)
Meningitis	1.2% (1/82)
Mental Status Changes	1.2% (1/82)
Pericardial Effusion	1.2% (1/82)
Phrenic Nerve Paralysis	1.2% (1/82)
Renal Failure Acute	1.2% (1/82)
Subdural Hematoma	1.2% (1/82)

Table 24. Serious adverse events occurring in experimental subjects, safety population

Serious Adverse Events	Experimental Subjects % (n / n) N=163
Pneumonia	2.5% (4/163)
Atrial Fibrillation	1.2% (2/163)
Deep Vein Thrombosis	1.2% (2/163)
Myocardial Infarction	1.2% (2/163)
Pulmonary Vein Stenosis	1.2% (2/163)
Asthenia	0.6% (1/163)
Asthma	0.6% (1/163)
Atrial Flutter	0.6% (1/163)
Cardiac Tamponade	0.6% (1/163)
Cardiopulmonary Failure	0.6% (1/163)
Escherichia Bacteremia	0.6% (1/163)
Gastrointestinal Hemorrhage	0.6% (1/163)
Ileitis	0.6% (1/163)
Multi Organ Failure	0.6% (1/163)
Pneumonitis	0.6% (1/163)
Pneumothorax	0.6% (1/163)
Pulmonary Embolism	0.6% (1/163)
Pyelonephritis Acute	0.6% (1/163)
Sepsis	0.6% (1/163)
Soft Tissue Hemorrhage	0.6% (1/163)
Subarachnoid Hemorrhage	0.6% (1/163)
Vessel Puncture Site Hematoma	0.6% (1/163)
Wegener S Granulomatosis	0.6% (1/163)

Death summary

No study subject died within 30 days of a cryoablation procedure. There was one death during the 12 month follow-up period. A 68 year old male Experimental Subject died shortly after a witnessed cardiac arrest occurring 10 months after cryoablation. The event was determined to be unrelated to the study devices, ablation procedure or approved anti-arrhythmic drug therapy.

Pulmonary vein stenosis

PV stenosis was defined by the study protocol as a 75% reduction in area which is roughly a 50% decrease in diameter. Assessment for PV dimensions was done at baseline of 6 and 12 months via CT/MRI scans. Seven of 228 (3.1%) cryoablated study subjects (5 ES and 2 Crossover CS) had one or more stenosed pulmonary veins (PVs) detected during study imaging. Two subjects were symptomatic and their pulmonary vein stenosis adverse events were adjudicated as SAEs and CPEs. Intervention was recommended for both subjects; one declined and the other had angioplasty and stenting with symptomatic improvement. Based on a multivariate analysis there are no known contributing factors to the incidence of PV stenosis.

Phrenic nerve injury

Cryoablation was associated with a high incidence of Transient Phrenic Nerve Dysfunction (TPND) occurring during procedures, which resolved by the end of the procedure and were almost always unassociated with subsequent phrenic nerve dysfunction. Phrenic nerve palsy (PNP), new onset hemi-diaphragmatic movement disorder detected by radiologic assessment, was found after 11.2% (29 / 259) of all cryoablation procedures of which 15 (51.7%) were asymptomatic. All but 4 cases resolved by the end of study follow-up, taking a mean of 158.2 days

(range 1 to 407). Three of 4 persistent PNP cases were symptomatic during follow-up, but none were disabling and only 1 persistent PNP subject had symptoms at the 12 Month visit. Based on a multivariate analysis there are no known contributing factors to the incidence of Phrenic Nerve Palsy.

Strokes and TIAs

Strokes occurred in 5 study subjects (4 ES and 1 CS); only one of these was related to a cryoablation procedure or the devices in a Crossover Control Subject. Of these 5 strokes, one was a subarachnoid hemorrhage from an anterior cerebral artery aneurysm, another was characterized as “whites spots in both eyes” and stroke could not be excluded, and one was a small lacunar stroke found incidentally during a work-up of dizziness. All 5 strokes recovered completely by the conclusion of study follow-up.

Esophageal injury

Esophageal ulcerations have been observed in some subjects who undergo cryoablation with the Arctic Front Cryoablation Catheter. As with other forms of left atrial ablation, the physician should consider appropriate medical strategies to minimize the risk of esophageal injury.

One (1) investigational center performed esophagogastroduodenoscopy post-cryoablation procedure on 12 STOP AF subjects. Of the 12 subjects, 3 were discovered to have esophageal ulcerations. All 3 subjects had follow-up esophagogastroduodenoscopy and demonstrated resolution of esophageal ulceration.

Vascular access complications

Other than routine cases of bruise, hematoma and discharge, there were 4 procedures (4 / 259, 1.5%) associated with significant vascular access site adverse events requiring surgical intervention or transfusion: 1 new AV fistula, 1 worsened pre-existing AV fistula, 2 pseudoaneurysms, and one hemorrhage requiring transfusion. One subject had both an AV fistula and a pseudoaneurysm.

5.9 Summary of STOP AF Pivotal Trial adverse events as categorized using MedDRA

There were a total of 1,406 adverse events (AEs) reported in 235 study subjects during the 12 month period of study follow-up. Seventy-six (76) CS experienced 485 AEs and 159 ES experienced 921 AEs. Ten (10) study subjects had no AEs reported, 6-CS and 4-ES.

In total, 69.2% (45/65) of Crossover CS and 75.5% (123/163) of ES experienced at least one **procedure-related AE**. Overall, the most frequently reported procedure-related AEs (higher than 10%) were back pain (35 subjects, 15.4%) and vessel puncture site hematoma (26 subjects, 11.4%). Other fairly common (higher than 5%) procedure-related AEs included pharyngolaryngeal pain (22 subjects,9.6%), cough (21 subjects, 9.2%), nausea (19 subjects, 8.3%), and procedural pain (15 subjects, 6.6%).

A greater proportion of ES (46.0%) experienced at least one device-related AE compared to Crossover CS (23.1%). The most frequently reported device-related AEs (higher than 10%) were in the following System Organ Class (SOC): Injury, Poisoning and Procedural Complications (Control:12.3%; Experimental: 18.4%), Nervous System Disorders (Control:13.8%; Experimental: 16.6%), Respiratory, Thoracic and Mediastinal Disorders (Control: 6.2%; Experimental: 12.3%), and General Disorders and Administration Site conditions (Control: 4.6%; Experimental: 11.0%). Overall, the only device-related AE occurring in greater than 10% of all cryoablated subjects was phrenic nerve paralysis (28subjects, 12.3%). Other common (higher than 5%) device-related AEs included nerve injury (22 subjects, 9.6%), cough (15 subjects, 6.6%) and venous injury (14 subjects, 6.1%). The majority of the device-related AEs that were observed occurred in less than 2% of subjects.

5.10 Study conclusion

The STOP AF Pivotal Trial demonstrated that there is a reasonable assurance of safety and effectiveness to support the use of the Arctic Front Cardiac Cryoablation Catheter, the Freezor MAX Cryocatheter, FlexCath Steerable Sheath and the CryoConsole (Gen V) in the treatment of patients with drug resistant paroxysmal atrial fibrillation.

6 Clinical summary update

Study title:	STOP AF PAS: Sustained Treatment of Paroxysmal Atrial Fibrillation Post Approval Study (STOP AF PAS)
Number of centers:	39 centers in the United States and Canada
Number of subjects:	402 enrolled subjects

Study purpose – The purpose of STOP AF PAS was to provide clinical evidence of long-term safety and effectiveness of the Arctic Front Cardiac Cryoablation Catheter System, including the Freezor MAX Cardiac Cryoablation Catheter according to the product labeling.[1]

The Arctic Front Cardiac Cryoablation Catheter is indicated for the treatment of drug refractory recurrent symptomatic paroxysmal atrial fibrillation.

6.1 Study design, study population, study visits, and length of follow-up

STOP AF PAS was a prospective multi-center, non-randomized, single arm, unblinded clinical study designed to provide long-term safety and effectiveness of the Arctic Front Cardiac Cryoablation System. The study was powered to test the primary effectiveness and safety hypotheses (i.e. treatment success > 45% at 36 months and frequency of cryoablation procedures events < 14.8% at 12 months post ablation). The study was conducted at 39 centers (32 in United States and 7 in Canada). Of these 39 centers, 6 centers previously participated in the STOP AF and/or CAP AF trials and 33 centers were new Arctic Front users.

Patients with drug refractory paroxysmal atrial fibrillation were considered for the study based on predefined inclusion and exclusion criteria.

Clinical data were required to be collected at baseline/enrollment, during the index ablation procedure, at the pre-discharge visit, and at any retreatments within the blanking period. The study protocol initially required that subjects be seen after the procedure for follow-up visits at 3, 6, and 12 months and 2, 3, 4, and 5 years, but was later amended to reduce the follow-up period to 3 years.

The STOP AF PAS required rhythm monitoring via:

- 12-lead ECG at the discharge, 3, 6, and 12 month, 2 and 3 year, and unscheduled visits
- 24-hour Holter monitoring at the 6 month visit
- 48-hour Holter monitoring at the 12 month, 2 and 3 year visits

6.2 Study endpoints

6.2.1 Primary Endpoints

6.2.1.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint was the rate of subjects free of chronic treatment failure (CTF) at 36 Months.

Chronic treatment failure was defined as:

- Documented atrial fibrillation lasting longer than 30 seconds (outside 90 day blanking period) or
- Intervention for atrial fibrillation (except for repeat cryoablation during the 90 day blanking period)

Intervention for atrial fibrillation was defined as:

- An invasive procedure intended for the definitive treatment of AF, including any ablation of the PVs or atrial triggers (other than protocol specified ablation), interruption of AV nodal function, procedures to alter left atrial conduction or function such as the Maze procedure, or the

[1] This study also included the next generation cryoballoon Arctic Front Advance Cardiac Cryoablation Catheter. Refer to Section 6.3 for enrollments details.

implantation of an atrial pacemaker or atrial defibrillator; whether approved by relevant regulatory authorities or not for such indications; excluding electrical or pharmacologic cardioversion of arrhythmias and excluding procedures solely directed at the treatment of atrial flutter or atrial tachycardias.

6.2.1.2 Primary Safety Endpoint

The primary safety endpoint was the rate of subjects experiencing one or more Cryoablation Procedure Events (CPE) through 12 months.

A CPE was defined as a device-related or procedure-related serious adverse event (SAE) with onset between the time of the subject's entry into the procedure room for the study-specified cryoablation procedure (Day 0) through the indicated onset intervals as set out in *Table 25*.

Table 25. Cryoablation Procedure Events

Cryoablation Procedure Events (CPE)	Onset Interval
Access site complications requiring:	
• Transfusion of 3 or more units or	Through 7 days
• Surgical intervention or	
• Permanent loss or functional impairment	
Cardiac damage (including MI) except for	Through 7 days
• Pulmonary vein stenosis[a]	Through 12 months
• Atrio-esophogeal fistula	Through 12 months
Embolic complications (including stroke)	Through 7 days
Arrhythmias	Through 7 days
• Persistent phrenic nerve palsy[b]	Through 12 months
Death	Through 7 days

[a] CPE was assessed at the completion of the follow-up visit, as determined by CT/MRI Core Lab.

[b] CPE was assessed at the completion of the follow-up as determined by chest X-ray (insp/exp)

6.2.2 Secondary Endpoints

Secondary objectives did not have pre-defined performance criteria but were included to provide additional detail on the performance of the Arctic Front Cardiac Cryoablation Catheter System.

6.2.2.1 Secondary Effectiveness Endpoint

Evaluate the proportion of subjects free of chronic treatment failure at the 1 and 2 year follow-up visits.

6.2.2.2 Secondary Safety Endpoint

Evaluate the proportion of subjects free of Major Atrial Fibrillation Events (MAFE) at the 1, 2, and 3 year follow-up visits.

A MAFE is defined a serious adverse event (SAE) — which has not been categorized as a CPE — as set out in *Table 26*

Table 26. Major Atrial Fibrillation Events

Major Atrial Fibrillation Events (MAFE)
Cardiovascular deaths
Hospitalizations for (primary reason):
AF recurrence or ablation
Atrial flutter ablation (excluding Type I)
Systemic embolization (not stroke)
Congestive heart failure
Hemorrhagic event (not stroke)
Antiarrhythmic drug: initiation, adjustment or complication
Myocardial infarction (MI)
Stroke

6.2.2.3 Long-term Safety Endpoint

Device and procedure related events, SAEs, unexpected adverse device effects and other safety categories collected through the 3 year follow-up and reported descriptively.

6.2.2.4 Cryoablation

Cryoablation procedure parameters will be summarized.

6.2.2.5 Procedure and Fluoroscopy Time

Total procedure time and total fluoroscopy time will be summarized.

6.2.2.6 Adverse Events

All adverse events will be summarized.

6.3 Total number of enrolled study sites and subjects, subject accountability and follow-up rate

Investigators at 39 sites enrolled a total of 402 study subjects of which 70 (17%) were enrolled from centers that previously participated in the STOP AF and/or CAP AF clinical studies, and 332 (83%) were enrolled from new Arctic Front user centers.

Study populations for analysis were:

- **Enrolled:** any patients who have a signed informed consent.
- **Intent-to-treat (ITT):** enrolled subjects that met all inclusion and no exclusion criteria.
- **Modified intent-to-treat (mITT):** Subjects within the ITT set with an Arctic Front Cardiac Cryoablation Catheter System inserted into the vasculature.
- **Modified ITT-AFA:** Subjects within the mITT set with an Arctic Front Advance catheter inserted into the vasculature.

Three hundred seventy (370) subjects were verified as meeting all inclusion and no exclusion criteria and are therefore considered the intent-to-treat (ITT) cohort under this protocol. Of the 370 ITT subjects, 354 met all eligibility criteria, were treated, and comprise the modified intent-to-treat (mITT) cohort. Of the 354 mITT subjects, 344 were treated with an Artic Front Advance cryoballoon and 10 were treated with an Arctic Front cryoballoon. The 344 mITT subjects treated with the Arctic Front Advance will be referred to as mITT-AFA.

Note: Not a pre-specified analysis population.

Subject accountability is described in *Table 27*.

Table 27. Subject disposition

Subject disposition	
Total Subjects Enrolled	N = 402
All inclusion/exclusion criteria met (ITT)	N = 370
All inclusion/exclusion criteria met and a study device inserted into vasculature (mITT)	N = 354
All inclusion/exclusion criteria met and subjects treated with Arctic Front Advance (mITT-AFA)	N = 344
Study complete (mITT cohort)	N = 303

Study exits for the mITT cohort are described in *Table 28*

Table 28. Study exits (mITT Cohort)

Exit timing	Exit Reason	N (%)
Exit prior to 36 months	Failure to maintain adequate study compliance	2 (0.6%)
	Investigator withdrew subject, other	1 (0.3%)
	Lost to follow-up	11 (3.1%)
	Other	1 (0.3%)
	Subject relocated to another geographic location	10 (2.8%)
	Subject requested withdrawal from the study, other	16 (4.5%)
	Subject withdrew consent	5 (1.4%)
Study completion through 3 years	Study completed	303 (85.6%)
Exit after 36 months	Subject requested withdrawal from the study, other	1 (0.3%)
Death	Death	4 (1.1%)[a]

[a] The Adverse Event Adjudication Committee (AEAC) adjudicated each of these events as not related to the procedure or system.

The number of mITT subjects that completed follow-up visits are listed in *Table 29*.

Table 29. Follow-up visits for mITT subjects

Visit Name	Length of CIP defined protocol window	Expected Visits	Visit Completion
3-month	28 days	354	344 (97.2%)
6-month	28 days	351	342 (97.4%)
12-month	30 days	343	325 (94.8%)
2-year	60 days	327	309 (94.5%)
3-year	30 days	308	298 (96.8%)

6.4 Baseline Characteristics

Baseline Characteristics are described in *Table 30*.

Table 30. Baseline Characteristics

	ITT (n = 370)	mITT (n = 354)
Gender (n,%)		
Male	246 (66.5%)	234 (66.1%)
Female	124 (33.5%)	120 (33.9%)
Age (years)		
Mean ± Standard Deviation	60.5±10.4	60.3± 10.5
Median	61	61
25th percentile – 75th percentile	54.0 – 68.0	54.0 – 68.0
Minimum – Maximum	27.0 – 82.0	27.0 – 82.0
Number of Subjects Reporting (N,%)	370 (100.0%)	354 (100.0%)
Race/Ethnic Origin (n,%)		
Subject/physician chose not to provide information	13 (3.5%)	13 (3.7%)
Not reportable per local laws or regulations	0 (0.0%)	0 (0.0%)
American Indian or Alaska Native	1 (0.3%)	1 (0.3%)
Asian	5 (1.4%)	5 (1.4%)
Black or African American	1 (0.3%)	1 (0.3%)
Hispanic or Latino	5 (1.4%)	4 (1.1%)
Native Hawaiian or Pacific Islander	1 (0.3%)	1 (0.3%)
White or Caucasian	343 (92.7%)	328 (92.7%)
Two or more races	0 (0.0%)	0 (0.0%)
Other race	1 (0.3%)	1 (0.3%)
Coronary Artery Disease	39 (10.5%)	34 (9.6%)
Hypertension	187 (50.5%)	176 (49.7%)
NYHA Functional Classification (N, %)		
No history of heart failure	295 (79.7%)	281 (79.4%)
Class I	53 (14.3%)	52 (14.7%)
Class II	22 (5.9%)	21 (5.9%)
Diabetes	37 (10.0%)	36 (10.2%)
Left Atrial Diameter (mm)		
Mean ± Standard Deviation	39.8 ± 5.7	39.8 ± 5.6
Median	40	40
Minimum – Maximum	23.0 – 60.0	23.0 – 60.0
Number of Subjects Reporting (N,%)	356 (96.2%)	342 (96.6%)
History of Atrial Flutter	102 (27.6%)	99 (28.0%)
Previous cardioversions (past 12 months)	119 (32.2%)	111 (31.4%)
Number of All Failed AADs (mean)[a]	1.3 ± 0.5	1.3 ± 0.5
AF episodes in the two months prior to enrollment (count)		
Mean ± Standard Deviation	18.6 ± 35.3	17.7 ± 33.3
Median	6	6
Minimum – Maximum	0.0 – 300.0	0.0 – 300.0
Number of Subjects Reporting (N,%)	362 (97.8%)	347 (98.0%)

[a] Based on ITT cohort of n=367 and mITT cohort of n=351; 3 subjects were not included in these analyses as the necessary records for specific prior failed AADs were missing. The site indicated all three subjects met the inclusion criterion of failing at least one membrane-active AAD for rhythm control prior to enrollment.

6.5 Repeat cryoballoon ablation during the blanking period

Eight (2.3%) subjects in the mITT cohort underwent repeat cryoballoon procedure within the 90-day blanking period. Of these 8 subjects, 3 were reported as chronic treatment failure (CTF); 5 mITT subjects with a repeat cryoablation procedure within the 90-day blanking period remained CTF free.

6.6 Rhythm monitoring compliance

A total of 2046 visits (1618 scheduled) required ECGs to be performed in mITT subjects, of which 1947 (95.2%) were completed. STOP AF PAS protocol did not require Holter monitoring at 3-month or unscheduled visits; 1274 of the 2046 visits required a Holter with overall compliance at 91.4%.

Table 31. Rhythm monitoring compliance in mITT subjects

Visit Name	Completed Visits	Holter Monitoring Compliance[b,c]	Holter Monitoring Before Scheduled Window[d]	Holter Completed Within or After Scheduled Window	ECG Compliance
3-Month	344	N/A	N/A	N/A	339 (98.5%)
6-Month	342	326 (95.3%)	26 (7.6%)	300 (87.7%)	340 (99.4%)

Table 31. Rhythm monitoring compliance in mITT subjects (continued)

Visit Name	Completed Visits	Holter Monitoring Compliance[b,c]	Holter Monitoring Before Scheduled Window[d]	Holter Completed Within or After Scheduled Window	ECG Compliance
12-Month	325	305 (93.8%)	42 (12.9%)	263 (80.9%)	323 (99.4%)
2-Year	309	276 (89.3%)	12 (3.9%)	264 (85.4%)	307 (99.4%)
3-Year	298	257 (86.2%)	49 (16.4%)	208 (69.8%)	295 (99.0%)
All Scheduled Visits	1618	1164 (91.4%)	129 (10.1%)	1035 (81.2%)	1604 (99.1%)
Unscheduled Visits	428	N/A	N/A	N/A	343 (80.1%)
All Visits	2046 (1274 requiring Holter)[a]	1164 (91.4%)	129 (10.1%)	1035 (81.2%)	1947 (95.2%)

[a] Because Holter monitoring was not required at 3-month and unscheduled follow-ups, mITT subjects completed a total of 1274 visit-required Holter monitors per the protocol. Holter compliance rates are calculated using 1274 visits as a denominator.

[b] Holter monitoring compliance is inclusive of completed monitoring outside of study visit window.

[c] Medtronic staff reviewed deviations for evidence of whether Holter monitoring was done for < 24 hours due to technical difficulties or operator error. Only two such instances were found: once at a 12-month follow-up and once at a 3-year visit. These were not counted as compliant in this table.

[d] Holter monitoring before scheduled window is defined as the start of Holter monitoring occurring prior to visit window opening. 129 Holter monitors were started before visit window. 14 of the 129 (10.9%) started prior to visit window, but the 24 or 48 hour duration overlapped and ended within the visit window. The remaining started and ended prior to the visit window open.

6.7 Results

6.7.1 Safety results

6.7.1.1 Primary Objective (Safety)

Definition: The primary safety objective was to demonstrate safety (through 12 months) of Arctic Front Cardiac Cryoablation Catheter System by assessing the rate of subjects experiencing a Cryoablation Procedure Event (CPE).

8 of the 354 mITT subjects reported a cryoablation procedure event (CPE) through 12 months. CPEs are listed in *Table 32*.

Table 32. Cryoballoon Procedure Event (CPE) details: mITT subjects

MedDRA Preferred Term (n = 354)	Number of Events (Number of subjects with event)
Cerebrovascular accident	1 (1)
Haematoma	1 (1)
Pericardial effusion	2 (2)
Phrenic nerve paralysis	3 (3)
Pulmonary vein stenosis	1 (1)
Sinus node dysfunction	1 (1)
Total	9 (8)[a]

[a] One subject was reported to experience both sinus dysfunction and PNI.

The Kaplan-Meier estimate of rate of CPE at 12 months was 2.3% [95% CI: 1.1% - 4.5%]. Because the upper 95% confidence bound (4.5%) is below the predefined performance criteria (14.8%), the primary safety objective is considered met.

6.7.1.2 Secondary Objective #2 (Safety)

Of the 354 mITT subjects, 77 unique subjects reported a total of 95 Major Atrial Fibrillation Events (MAFEs) through 36 months. MAFEs are listed in *Table 33*.

Table 33. Major Atrial Fibrillation Events

Major Atrial Fibrillation Events (MAFEs):		
MAFE category	MedDRA Preferred term	Number of Events (Number of Subjects with event)
Cardiovascular deaths		0 (0)
Hospitalizations for AF recurrence or ablation	Atrial fibrillation	60 (54)
	Atrial tachycardia	1 (1)
	Sinus node dysfunction	1 (1)
Hospitalizations for atrial flutter ablation	Atrial fibrillation	2 (2)
	Atrial flutter	11 (11)
Hospitalizations for Systemic embolization (not stroke)		0 (0)
Hospitalization for congestive heart failure	Cardiac failure congestive	2 (2)
	Cardiomyopathy	1 (1)
Hospitalization for Hemorrhagic event (not stroke)	Brain stem hemorrhage	1 (1)
	Cerebral hemorrhage	1 (1)
	Hemorrhage intracranial	1 (1)
	Subdural hematoma	1 (1)
Hospitalization for Antiarrhythmic drug: initiation, adjustment or complication	Atrial fibrillation	7 (7)
	Atrial flutter	3 (3)
Myocardial infarction (MI)		2 (2)
Stroke	Cerebrovascular Accident	1 (1)

The Kaplan-Meier estimate of freedom from MAFE at 1, 2, and 3 years are:

- 12 months = 90.3% [95% CI: 86.6% - 92.9%]
- 24 months = 83.2% [95% CI: 78.8% - 86.8%]
- 36 months = 77.8% [95% CI: 72.9% - 81.9%]

6.7.1.3 Secondary Objective #3 (Long-Term Safety)

No unexpected adverse device effects (UADE) were reported. The Kaplan-Meier estimates of freedom from adverse events are:

Device related:

- 12 months = 86.7% [95% CI: 82.3% - 89.6%]
- 24 months = 84.9% [95% CI: 80.3% - 87.9%]
- 36 months = 82.9% [95% CI: 76.5% - 85.8%]

Procedure related:

- 12 months = 67.8% [95% CI: 62.6% - 72.4%]
- 24 months = 66.6% [95% CI: 61.4% - 71.2%]
- 36 months = 65.2% [95% CI: 60.0% - 70.0%]

Serious adverse event:

- 12 months = 76.9% [95% CI: 71.8% - 80.7%]
- 24 months = 66.2% [95% CI: 60.6% - 70.7%]
- 36 months = 59.5% [95% CI: 53.6% - 64.2%]

6.7.2 Effectiveness results

6.7.2.1 Primary Efficacy Objective

The primary effectiveness endpoint was the rate of subjects free of chronic treatment failure (CTF), defined as AF recurrence of at least 30 seconds after the 90-day blanking period through 3 years or intervention for atrial fibrillation (except for repeat cryoablation during the 90-day blanking period), at 36 months.

Of the 354 mITT subjects, 114 reported a CTF; 111 occurred prior to 36 months post index ablation, and 3 occurred after 36 months. The freedom from CTF at 36 months was 66.9% [95% CI: 61.6 - 71.7%]. As the lower 95% confidence bound (61.6%) was above the predefined performance criteria (45%), the primary effectiveness objective was considered met.

Figure 4 displays the Kaplan-Meier curve for freedom from chronic treatment failure for mITT subjects (n=354) through 36 months post procedure. The solid line is the Kaplan-Meier estimate, and the dashed lines are the 95% confidence interval. Kaplan-Meier estimate and 95% confidence interval at 36 months post procedure are reported in *Table 34*.

Figure 4. Freedom from Chronic Treatment Failure in mITT subjects at 36 Months

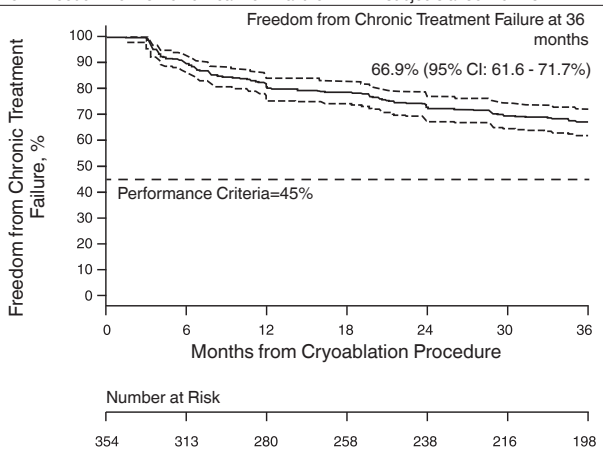


Table 34. Chronic treatment success in mITT subjects at 36 months

Months Since Treatment (n=354)	Kaplan-Meier Rate [95% CI]
36 months	66.9% [95% CI: 61.6 - 71.7%]

Table 35. Primary reason for chronic treatment failure (mITT cohort)

Total number of mITT subjects = 354	Year 1	Year 2	Year 3
Cumulative number of subjects with chronic treatment failure	68	93	111
Documented atrial fibrillation ≥ 30 seconds	58 (85.3%)	79 (84.9%)	96 (86.5%)
Repeat ablation after the 90-day blanking period	9 (13.2%)	13 (14.0%)	14 (12.6%)
RF treatment of atrial fibrillation within 90-day blanking period	1 (1.5%)	1(1.1%)	1 (0.9%)

Table 36. Use of Membrane-Active Atrial Fibrillation Drugs (AFDs) and DC Cardioversion (DCCV)

Total number of mITT subjects	**354**
Total number of successes (no chronic treatment failure)	**243**
Total number of successes who received AFD or DCCV post 90-day blanking period [Count (% of mITT subjects, % of successes)]	**78 (22.0%,32.1%)**
AFD initiated before index procedure and continued beyond 90-day blanking period [Count (% of mITT subjects, % of successes)]	43 (12.1%, 17.7%)
AFD initiated during blanking period and continued beyond 90-day blanking period [Count (% of mITT subjects, % of successes)]	22 (6.2%, 9.1%)
AFD initiated after 90-day blanking period [Count (% of mITT subjects, % of successes)]	12 (3.4%, 4.9%)
AFD initiated 91 – 365 days postprocedure (no DCCV)	9 (2.5%, 3.7%)
AFD initiated 366 – 730 days postprocedure (no DCCV)	1 (0.3%, 0.4%)
AFD initiated > 730 days postprocedure (no DCCV)	2 (0.6%, 0.8%)
AFD initiated before index procedure and continued beyond 90-day blanking period, and DCCV post 90-day blanking period [Count (% of mITT subjects, % of successes)]	1 (0.3%, 0.4%)[a]

[a] Subject was on AFD prior to enrollment, had asymptomatic AF recurrence 21 days into the blanking period, and had a DCCV at day 100.

6.7.2.2 Secondary Objective #1 (Efficacy)

The secondary effectiveness endpoint was to evaluate the proportion of subjects free of chronic treatment failure at the 1 and 2 year follow-up visits. Of the 354 mITT subjects, 68 subjects reported a CTF within the first year and 25 subjects reported a CTF between the first and second year. The freedom from chronic treatment failure (see definition in Section 6.7.2.1) at 1 year was 80.4% [95% CI: 75.9%, 84.2%], and at 2 years was 72.8% [95% CI: 67.7%, 77.2%].

Table 37. Chronic Treatment Success in mITT Subjects at 1 and 2 Years

Years Since Treatment (n=354)	Kaplan-Meier Rate [95% CI]
1 year	80.4% [75.9%, 84.2%]
2 years	72.8% [67.7%, 77.2%]

6.7.2.3 Single Procedure Success

A post hoc analysis was performed to evaluate single procedure success. Single procedure success was defined as freedom from chronic treatment failure (CTF) without repeat cryoablation procedure within the blanking period. Overall, single procedure success was observed in 238 of 354 (67%) mITT subjects at 36 months.

Table 38. Single procedure success

	Freedom from Chronic Treatment Failure		Single Procedure Success Rate	
	Number of Failures	KM Rate (95% CI)	Number of Failures	KM Rate (95% CI)
12 months	68	80.4% (75.9 - 84.2%)	73	79.0% (74.3 – 82.9%)
24 months	93	72.8% (67.7 - 77.2%)	98	71.3% (66.2 – 75.8%)
36 months	111	66.9% (61.6 - 71.7%)	116	65.5% (60.1 – 70.3%)

6.7.2.4 Post Hoc Analysis of Efficacy at 36 Months (mITT-AFA cohort)

Of the 344 mITT- AFA subjects, 104 reported an AF recurrence of at least 30 seconds after the 90-day blanking period through 3 years, and 117 mITT- AFA subjects reported an AF/AFL/AT recurrence of at least 30 seconds after the 90-day blanking period through 3 years. Freedom from AF recurrence and AF/AFL/AT recurrence for mITT- AFA subjects (those subjects treated with Arctic Front Advance) are included in *Table 39*

Table 39. Freedom from AF recurrence and AF/AFL/AT recurrence through 3 years

	Rate of Freedom From AF recurrence [95% CI]	Rate of Freedom From AF/AFL/AT recurrence [95% CI]
36 months	68.1% (62.7 – 72.9%)	64.1% (58.6 – 69.1%)

6.7.2.5 Post Hoc Analysis of Efficacy at 12 and 24 months (mITT-AFA cohort)

Of the 344 mITT-AFA subjects, 62 reported an AF recurrence of at least 30 seconds after the 90-day blanking period through 1 year, and 71 reported an AF/AFL/AT recurrence of at least 30 seconds after the 90-day blanking period through 1 year; 87 reported an AF recurrence of at least 30 seconds after the 90-day blanking period through 2 years, and 97 reported an AF/AFL/AT recurrence of at least 30 seconds after the 90-day blanking period through 2 years. Freedom from AF recurrence and AF/AFL/AT recurrence at 1 year and 2 years for mITT-AFA subjects (those subjects treated with Arctic Front Advance) are included in *Table 40*.

Table 40. Freedom from AF recurrence and AF/AFL/AT recurrence through 1 year and 2 years

	Rate of Freedom From AF recurrence [95% CI]	Rate of Freedom From AF/AFL/AT recurrence [95% CI]
12 months	81.6% (77.1 – 85.4%)	79.0% (74.2 – 82.9%)
24 months	73.8% (68.6 – 78.2%)	70.8% (65.5 – 75.4%)

6.7.3 Additional results

6.7.3.1 Secondary Objective #4 (Cryoablation):

All 354 mITT subjects underwent pulmonary vein ablation with a Cryoballoon. The following data are derived from index procedures only.

- 31 (8.8%) were treated with a 23 mm balloon size
- 314 (88.7%) were treated with a 28 mm balloon size
- 9 (2.5%) were treated with both a 23 mm and 28 mm balloon size

Average number of cryoballoon applications per pulmonary vein was:

- 23 mm: 2.1 ± 1.0
- 28 mm: 2.4 ± 1.2

Average temperature (Celsius) observed during a cryoballoon application was:

- 23 mm: -51.4 ± 14.9
- 28 mm: -45.5 ± 11.7

Average duration of cryoballoon application on a pulmonary vein was:

- 23 mm: 184.2 ± 78.7 seconds
- 28 mm: 200.2 ± 60.8 seconds

25 of 354 (7.1%) mITT subjects had additional focal pulmonary vein ablation

- 4 (1.1%) were treated with a focal cryocatheter
- 21 (5.9%) were treated with a focal radiofrequency (RF) catheter

6.7.3.2 Secondary Objective #5 (Procedure and Fluoroscopy time):

The following data are derived from index procedures only.

Average total procedure time was 232.1 ± 72.6 minutes.

Average total fluoroscopy time was 20.0 ± 12.0 minutes.

6.7.3.3 Secondary Objective #6 (Summary of Adverse Events)

Adverse events occurring during the study were continuously monitored and collected. All adverse events in all enrolled subjects are summarized below. There were no Unanticipated Adverse Device Effects reported in the STOP AF PAS. A total of 957 adverse events have been reported in the study. All 957 events were adjudicated by the Adverse Event Adjudication Committee (AEAC). For adverse event analysis, the AEAC determination of seriousness and relatedness status was used.

A total of six (6) adverse events had an outcome of death. One (1) death occurred in a subject prior to procedure, and five (5) deaths occurred post-procedure: four (4) in mITT subjects, and one (1) in a subject for whom inclusion/exclusion criteria were not met. The AEAC adjudicated each of these events as not related to the procedure or system.

A total of 390 subjects enrolled in this study were considered to be at risk for an adverse event prior to an ablation procedure being performed (all 402 enrolled subjects, excluding 6 subjects rolled over from the CAP-AF/STOP AF studies and 6 subjects with incomplete data from a center that was closed early). Adverse event frequency prior to ablation procedure is reported in *Table 41*. Prior to an ablation procedure, there were 12 subjects (3.1%) who had a total of 15 adverse events.

Table 41. Adverse Events Occurring Prior to Ablation Procedure by MedDRA Preferred Term

	Number of Events (Number, % of Subjects) Total Subjects (N = 390)
Adverse Events	**Events**
Keyterm	
Atrial fibrillation	3 (2, 0.5%)
Acute respiratory failure	1 (1, 0.3%)
Adverse drug reaction	1 (1, 0.3%)
Atrial thrombosis	1 (1, 0.3%)
Diabetic retinal oedema	1 (1, 0.3%)
Diverticulum	1 (1, 0.3%)
Haematuria	1 (1, 0.3%)
Headache	1 (1, 0.3%)
Immune thrombocytopenic purpura	1 (1, 0.3%)
Medication error	1 (1, 0.3%)
Pain in extremity	1 (1, 0.3%)
Sleep apnoea syndrome	1 (1, 0.3%)

Table 41. Adverse Events Occurring Prior to Ablation Procedure by MedDRA Preferred Term (continued)

Syncope	1 (1, 0.3%)
Total Adverse Events	15 (12, 3.1%)

There were 359 subjects who underwent cryoablation for this study; 354 subjects met all inclusion and exclusion criteria (mITT cohort), and 5 subjects were treated but did not meet all inclusion and exclusion criteria. Additionally, 6 subjects underwent cryoablation prior to this protocol (rollover subjects from the STOP AF/CAP AF studies), of which one subject reported an adverse event (hypertension) 1831 days post-ablation. AEs in the 359 treated subjects are summarized below. A summary of the relatedness to the procedure or to any component of the system (including the Balloon cryocatheter, Focal cryocatheter, FlexCath Sheath, CryoConsole, Manual retraction kit, or other) and seriousness are provided in *Table 42*.

Table 42. Relatedness of Adverse Events Occurring During or After Ablation Procedure

Adverse Event Classifications	**Number of Events (Number, % of Subjects) Total Subjects (N = 359)**
Relationship to Procedure	
Not related	741 (270, 75.2%)
Related	195 (126, 35.1%)
Unknown	4 (4, 1.1%)
Missing	0 (0, 0.0%)
Relationship to Device	
Not related	824 (277, 77.2%)
Related	75 (60, 16.7%)
Unknown	41 (35, 9.7%)
Missing	0 (0, 0.0%)
Serious	
Yes	261 (145, 40.4%)
Device related	49 (41, 11.4%)
Procedure related	26 (24, 6.7%)
No	679 (255, 71.0%)
Total Adverse Events	940 (293, 81.6%)

The frequency of serious adverse events is displayed in *Table 43*. A total of 145 of 359 subjects (40.4%) reported a serious adverse event. The most common serious adverse event was atrial fibrillation, reported in 15.6% (56/359) subjects. Of all 957 observed AEs, 940 occurred in the 359 treated subjects (summarized in *Table 42*) on or after the index ablation date; 15 occurred prior to ablation (*Table 41*); one occurred in a CAP-AF rollover subject, and one was a CPE which occurred in a subject with incomplete data from a center that was closed early.

Table 43. Serious Adverse Events Occurring During or After Ablation Procedure by Key Term

		Number of Events (Number, % of Subjects) Total Subjects (N = 359)	
Adverse Events	**Events**	**Device Related**	**Procedure Related**
Keyterm			
Atrial fibrillation	75 (65, 18.1%)	1 (1, 0.3%)	1 (1, 0.3%)
Atrial flutter	20 (20, 5.6%)	14 (14, 3.9%)	12 (12, 3.3%)
Osteoarthritis	9 (8, 2.2%)	0 (0, 0.0%)	0 (0, 0.0%)
Coronary artery disease	5 (3, 0.8%)	0 (0, 0.0%)	0 (0, 0.0%)
Urinary tract infection	5 (5, 1.4%)	3 (3, 0.8%)	0 (0, 0.0%)
Cardiac failure congestive	4 (4, 1.1%)	1 (1, 0.3%)	0 (0, 0.0%)
Meniscus injury	4 (4, 1.1%)	0 (0, 0.0%)	0 (0, 0.0%)
Acute myocardial infarction	3 (3, 0.8%)	1 (1, 0.3%)	0 (0, 0.0%)
Phrenic nerve paralysis	3 (3, 0.8%)	3 (3, 0.8%)	3 (3, 0.8%)
Post procedural haemorrhage	3 (3, 0.8%)	2 (2, 0.6%)	2 (2, 0.6%)
Sinus node dysfunction	3 (3, 0.8%)	1 (1, 0.3%)	1 (1, 0.3%)
Anaemia	2 (2, 0.6%)	0 (0, 0.0%)	0 (0, 0.0%)
Angina pectoris	2 (2, 0.6%)	1 (1, 0.3%)	0 (0, 0.0%)
Angina unstable	2 (2, 0.6%)	0 (0, 0.0%)	0 (0, 0.0%)
Atelectasis	2 (2, 0.6%)	0 (0, 0.0%)	0 (0, 0.0%)
Atrial tachycardia	2 (2, 0.6%)	2 (2, 0.6%)	2 (2, 0.6%)
Bradycardia	2 (2, 0.6%)	1 (1, 0.3%)	1 (1, 0.3%)
Cerebrovascular accident	2 (1, 0.3%)	2 (1, 0.3%)	0 (0, 0.0%)
Chest pain	2 (2, 0.6%)	0 (0, 0.0%)	0 (0, 0.0%)
Cholangitis	2 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Diverticulitis	2 (2, 0.6%)	0 (0, 0.0%)	0 (0, 0.0%)
Dyspnoea	2 (2, 0.6%)	0 (0, 0.0%)	0 (0, 0.0%)
Haematoma	2 (2, 0.6%)	2 (2, 0.6%)	2 (2, 0.6%)
Inguinal hernia	2 (2, 0.6%)	0 (0, 0.0%)	0 (0, 0.0%)
Mental status changes	2 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Pancreatitis	2 (2, 0.6%)	0 (0, 0.0%)	0 (0, 0.0%)
Pericardial effusion	2 (2, 0.6%)	2 (2, 0.6%)	0 (0, 0.0%)
Prostate cancer	2 (2, 0.6%)	0 (0, 0.0%)	0 (0, 0.0%)
Pulmonary vein stenosis	2 (2, 0.6%)	2 (2, 0.6%)	1 (1, 0.3%)
Spinal column stenosis	2 (2, 0.6%)	0 (0, 0.0%)	0 (0, 0.0%)
Squamous cell carcinoma	2 (2, 0.6%)	0 (0, 0.0%)	0 (0, 0.0%)
Accidental death	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Acute kidney injury	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Acute respiratory failure	1 (1, 0.3%)	1 (1, 0.3%)	1 (1, 0.3%)
Allergy to arthropod sting	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Aortic stenosis	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Aortic valve stenosis	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Basal cell carcinoma	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Bladder adenocarcinoma stage unspecified	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Brain stem haemorrhage	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Breast cancer recurrent	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Bronchitis	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Bronchitis viral	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
CHA2DS2-VASc annual stroke risk moderate	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Calculus ureteric	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Cardiac failure	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Cardiomyopathy	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Carpal tunnel syndrome	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Catheter site haemorrhage	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Cauda equina syndrome	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Cellulitis	1 (1, 0.3%)	1 (1, 0.3%)	0 (0, 0.0%)
Cerebral haemorrhage	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Cervical spinal stenosis	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)

Table 43. Serious Adverse Events Occurring During or After Ablation Procedure by Key Term (continued)

Cholecystitis	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Cholecystitis infective	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Cholelithiasis	1 (1, 0.3%)	1 (1, 0.3%)	0 (0, 0.0%)
Chronic obstructive pulmonary disease	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Clostridium difficile colitis	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Clostridium difficile infection	1 (1, 0.3%)	1 (1, 0.3%)	0 (0, 0.0%)
Colitis microscopic	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Colon cancer	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Colostomy closure	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Constipation	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Death	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Diverticular perforation	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Escherichia bacteraemia	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Fall	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Forearm fracture	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Gastric cancer	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Gastrointestinal haemorrhage	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Generalised tonicclonic seizure	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Glaucoma	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Haemoptysis	1 (1, 0.3%)	1 (1, 0.3%)	0 (0, 0.0%)
Haemorrhage intracranial	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Hip fracture	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Hypersensitivity	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Hypotension	1 (1, 0.3%)	1 (1, 0.3%)	0 (0, 0.0%)
Ileus	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Knee arthroplasty	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Lymphadenopathy	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Migraine	1 (1, 0.3%)	1 (1, 0.3%)	0 (0, 0.0%)
Mitral valve calcification	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Multiple sclerosis	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Nephrolithiasis	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Neuralgia	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Nodal rhythm	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Non-cardiac chest pain	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Obesity	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Osteonecrosis	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Osteoporosis	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Pericarditis	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Periprosthetic fracture	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Plasma cell leukaemia	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Pleural effusion	1 (1, 0.3%)	1 (1, 0.3%)	0 (0, 0.0%)
Pneumonia	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Pneumonia bacterial	1 (1, 0.3%)	1 (1, 0.3%)	0 (0, 0.0%)
Post procedural bile leak	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Post procedural pneumonia	1 (1, 0.3%)	1 (1, 0.3%)	0 (0, 0.0%)
Procedural pain	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Psychotic disorder	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Pulmonary mass	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Rectal haemorrhage	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Retinal detachment	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Sepsis	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Small intestinal obstruction	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Spinal compression fracture	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Spinal osteoarthritis	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Squamous cell carcinoma of skin	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Subdural haematoma	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Thyroid cancer	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Toxicity to various agents	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Transient global amnesia	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Trigger finger	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Umbilical hernia	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Urosepsis	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Vascular pseudoaneurysm	1 (1, 0.3%)	1 (1, 0.3%)	0 (0, 0.0%)
Ventricular tachycardia	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Vitreous detachment	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Total Adverse Events	**261 (145, 40.4%)**	**49 (41, 11.4%)**	**26 (24, 6.7%)**

6.8 Study strengths and weaknesses

The following points cover the major strengths and weaknesses of the study.

Strengths:

- This large, prospective, multicenter study had sufficient statistical power to test the primary effectiveness and safety hypotheses
- This study provided long term (3-year) effectiveness and safety data on cryoballoon ablation of paroxysmal AF
- Real world perspective (both experienced and new cryoablation users included)
- Independent adjudication of all safety and effectiveness events
- Core Lab for PV stenosis assessments
- Same arrhythmia monitoring methods required for all subjects

Weaknesses:

- Single arm study/ no control group
- The rhythm monitoring employed in the study was limited to periodic ECG and Holter monitoring as well as submission of documented episodes of AF that occurred outside of the protocol-required ECGs and Holters. Therefore, AF episodes that occurred in between the scheduled ECGs/Holters but that were not documented could have been missed. Moreover, the study protocol did not require discontinuation of class I/III AADs after the 3-month blanking period. Instead, the use of class I/III AADs was at the discretion of the investigators. As a result, approximately one-fifth of study subjects were on a class I or III AAD after the 3- month blanking period. All these may have resulted in an overestimation of the effectiveness of cryoballoon ablation in the paroxysmal AF population.

7 Clinical summary update

Study title:	STOP Persistent AF
Number of centers:	22 centers in the United States and Canada
Number of subjects:	169 enrolled and 150 treated subjects in the US and Canada

Study purpose – The purpose of STOP Persistent AF was to demonstrate the safety and effectiveness of the Arctic Front Advance and Freezor MAX Cardiac CryoAblation Catheters for the treatment of symptomatic drug refractory recurrent persistent atrial fibrillation (AF).

7.1 Study design, study population, study visits, and length of follow-up

STOP Persistent AF was a prospective, interventional, multi-center, non-randomized, single arm, unblinded clinical study conducted at 22 centers (19 in United States and 3 in Canada). The first study subject was enrolled in March 2017 and the last subject enrolled in July 2018.

Subjects with drug refractory symptomatic persistent atrial fibrillation of less than 6 months duration were considered for the study based on predefined inclusion and exclusion criteria and underwent pulmonary vein (PV) isolation using the Arctic Front Advance and Freezor MAX Cardiac CryoAblation Catheters. Subjects were followed for 12 months post procedure to assess adverse events and recurrence of atrial tachyarrhythmias.

Clinical data were required to be collected at baseline/enrollment, during the index ablation procedure, at the pre-discharge visit, 6 weeks, 3 months, 6 months and 12 months post ablation, and at any repeat ablations.

The STOP Persistent AF study required rhythm monitoring via:

- 12-lead ECG at baseline, discharge, 3, 6, and 12 months, and unscheduled visits
- 24-hour Holter monitoring at the 6- and 12-month visits
- Trans-telephonic monitoring (TTM) starting at 3 months, weekly and upon symptoms

A core lab was utilized to review tracings from 12-lead ECG, 24-hour Holter and TTM for the adjudication of atrial arrhythmias for the primary effectiveness endpoint evaluation.

An independent Clinical Events Committee (CEC) was utilized to review and adjudicate all device-related and all procedure-related adverse events, as well as all deaths for the primary safety endpoint evaluation.

The study would be considered successful if the pre-defined performance goals for both the primary safety and effectiveness endpoints are met. The performance goal for the primary effectiveness endpoint was set to 40%, and the performance goal for the primary safety endpoint was set to 13%.

7.2 Study endpoints

7.2.1 Primary Endpoints

7.2.1.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint was the proportion of subjects free of treatment failure at 12 months after the PVI ablation procedure.

Treatment success was defined as freedom from treatment failure. Treatment failure was defined as any of the following components:

- Acute procedural failure
- Documented AF/AT/AFL on Holter/TTM/12-lead ECG after the 90-day blanking period
  - Minimum of 30 seconds on Holter/TTM and 10 seconds on 12-lead ECG
- A re-ablation for the treatment of recurrent AF/AT/AFL after the 90-day blanking period
- Class I or III antiarrhythmic drug (AAD) dose increase from the historic maximum ineffective dose (prior to the ablation procedure) or initiation of a new Class I or III AAD after the 90-day blanking period. Note: remaining on the same pre-ablation dose or decreased dose, or re-initiation of a previously failed or not tolerated Class I or III AAD after the 90-day blanking was not considered a failure. Subjects were allowed to remain on Class I or III antiarrhythmic medications at the historic maximum ineffective dose (on prior to the ablation procedure) after the 90-day post-procedure blanking period.
- Ablation using RF in the left atrium

Blanking period was defined as the first 90 days after the index ablation procedure. Recurrences of atrial arrhythmias during the blanking period were not counted in the determination of the first clinical failure for the primary endpoint. Within the blanking period, recurrent arrhythmias could be managed with antiarrhythmic drugs, cardioversion or one cryo re-ablation procedure of the pulmonary veins. Titration of Class I and III antiarrhythmic medications was allowed during the blanking period.

Acute procedural failure was defined as:

- Inability to isolate all accessible targeted pulmonary veins (minimally assessed for entrance block and, where assessable, exit block) during the index procedure; OR
- Left atrial non-PVI ablations including but not limited to, ablation of linear lesions, complex fractionated electrograms or non-PV triggers

7.2.1.2 Primary Safety Endpoint

The primary safety endpoint was the proportion of subjects experiencing one or more primary safety events.

A primary safety event was defined as a serious procedure-related or serious system-related adverse event including the following:

- Transient ischemic attack (within 7 days of ablation procedure)
- Cerebrovascular accident (within 7 days of ablation procedure)
- Major bleeding that requires transfusion (within 7 days of ablation procedure)
- Cardiac perforation, tamponade or pericardial effusion (within 7 days of ablation procedure)
- Pulmonary vein stenosis (>75% reduction within 12-months of ablation procedure)
- Myocardial infarction (within 7 days of ablation procedure)
- Phrenic nerve injury (unresolved at 12-months)
- Atrio-esophageal fistula (within 12-months of ablation procedure)
- Death (within 7 days of ablation procedure)

7.2.2 Secondary Endpoint

The secondary endpoint was the improvement in quality of life between baseline and 12 months as measured by the Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) and SF-12 questionnaires.

7.2.3 Ancillary Endpoint

7.2.3.1 Acute Procedural Success

Acute procedural success was the opposite of acute procedural failure.

7.2.3.2 12-month single procedure success

The same definition as the primary effectiveness endpoint was utilized for 12-month single procedure success, with the additional component that if an ablation occurred during the blanking period, those subjects were set to treatment failure at the date of the blanking period ablation.

7.2.3.3 Procedure measurements

Total procedure time, left atrial dwell time, fluoroscopy time, and application duration were summarized.

7.2.3.4 Treatment success in subjects off Class I and III AADs

This ancillary endpoint compared treatment success in subjects on vs. those off Class I and Class III AADs on day 90 post procedure. The same definition as the primary effectiveness endpoint was utilized for treatment failure.

7.2.3.5 Atrial arrhythmias present and/or treated

All atrial arrhythmias present and/or treated during the cryoablation procedure were summarized.

7.2.3.6 All Adverse Events

All adverse events were summarized.

7.3 Total number of enrolled study sites and subjects, subject accountability and follow-up rate

Investigators at 22 sites in the United States and Canada enrolled a total of 169 subjects of which 150 were treated with an Artic Front Advance cryoballoon. Study populations for analysis were:

- **Enrolled:** Any patients who have a signed informed consent.
- **Modified intent-to-treat (mITT):** Enrolled subjects who maintained informed consent at least until the index cryoablation procedure was finished.

One hundred sixty-nine (169) subjects signed a study informed consent form and were therefore considered the enrolled cohort under this protocol. Of the 169 enrolled subjects, 150 maintained informed consent through the index ablation procedure and thus comprised the modified intent-to-treat (mITT) cohort. All 150 mITT subjects were treated with an Artic Front Advance cryoballoon.

Subject accountability is described in *Table 44*.

Table 44. Subject disposition

Subject disposition	
Total Subjects Enrolled	N = 169
All inclusion/exclusion criteria met and subjects treated with Arctic Front Advance (mITT)	N = 150
Study completed (mITT)	N = 130

Study exits for the mITT cohort are described in *Table 45*

Table 45. Study exits (mITT Cohort)

Number of Subjects Treated (N=150)	
Exit Post-Procedure, Prior to 12 Month Visit	20 (13.3%)
Lost to Follow-Up	6
Subject Requested Withdrawal	6
Other Post-Procedure Exit	8
Completed 12 Months/Study Completed	130 (86.7%)
Death	0 (0.0%)

The number of mITT subjects that completed follow-up visits are listed in *Table 46*.

Table 46. Follow-up visits for mITT subjects

Visit Name	**Length of CIP defined protocol window**	**Expected Visits**	**Visit Completion**
6-week phone call	7 days	150	149 (99.3%)
3-month	30 days	148	144 (97.3%)
6-month	30 days	143	134 (93.7%)
12-month	30 days	140	130 (92.9%)

7.4 Baseline Characteristics

Baseline Characteristics are described in *Table 47*.

Table 47. Baseline Characteristics

	mITT (n = 150)
Sex (N,%)	
Male	105 (70.0%)
Female	45 (30.0%)
Not reported	0 (0.0%)
Age (years)	
Mean ± Standard Deviation	65 ± 9
Median	66
25th percentile – 75th percentile	59 – 72
Minimum – Maximum	38 – 88
Not reported (%)	0 (0%)
Baseline BMI	
Mean ± Standard Deviation	31 ± 6
Median	30
25th percentile – 75th percentile	27 – 35
Minimum – Maximum	17 – 61[a]
Not reported (%)	0 (0%)
Race/Ethnic Origin (N,%)	
White or Caucasian	142 (94.7%)
Subject/physician chose not to provide information	4 (2.7%)
Black	2 (1.3%)
Filipino	1 (0.7%)
Other Asian	1 (0.7%)
Time from First Diagnosis of Persistent AF (years)	
Mean ± Standard Deviation	0.6 ± 1.4
Median	0.2
25th percentile – 75th percentile	0.1 – 0.5
Minimum – Maximum	0.0 – 9.9
Duration of Longest Persistent AF Episode (days)	
Mean ± Standard Deviation	70.9 ± 49.7
Median	60.9
25th percentile – 75th percentile	30.0 – 95.0
Minimum – Maximum	7.0 – 182.6
Number of Prior Cardioversions	
Mean ± Standard Deviation	2.1 ± 2.3
Median	2.0
25th percentile – 75th percentile	1.0 – 3.0
Minimum – Maximum	0.0 – 21.0
Not reported (%)	0 (0.0%)
Cardioversion prior to enrollment	**121 (80.7%)**
Electrical	120 (80.0%)
Pharmacological	15 (10.0%)
Number of Failed Class I/III AADs	
Mean ± Standard Deviation	1.2 ± 0.6
Median	1.0

Table 47. Baseline Characteristics (continued)

	mITT (n = 150)
25th percentile – 75th percentile	1.0 – 1.0
Minimum – Maximum	0.0 – 3.0
Not reported (%)	0 (0.0%)
History of Atrial Flutter (N,%)	
Yes	28 (18.7%)
No	122 (81.3%)
History of Atrial Tachycardia (N,%)	
Yes	3 (2.0%)
No	147 (98.0%)
AF/AT/AFL Symptoms	
Palpitations	98 (65.3%)
Fatigue/Weakness	97 (64.7%)
Dyspnea	95 (63.3%)
Dizziness	46 (30.7%)
Rapid heart beat	33 (22.0%)
Syncope	7 (4.7%)
Other symptoms	51 (34.0%)
None	0 (0.0%)
Left Ventricular Ejection Fraction (%)	
Mean ± Standard Deviation	56 ± 6
Median	55
25th percentile – 75th percentile	54 – 60
Minimum – Maximum	36 – 71
Not reported (%)	0 (0%)
Left Atrial Diameter (cm)	
Mean ± Standard Deviation	4.2 ± 0.6
Median	4.4
25th percentile – 75th percentile	3.8 – 4.7
Minimum – Maximum	2.4 – 5.0
Not reported (%)	3 (2.0%)
Medical History	
Coronary Artery Disease	18 (12.0%)
Myocardial Infarction	7 (4.7%)
Hypertension	93 (62.0%)
Prior Cardiac Valvular Surgery	1 (0.7%)
Diabetes	19 (12.7%)
Congestive Heart Failure	31 (20.7%)
Stroke or TIA	6 (4.0%)
Renal Insufficiency	8 (5.3%)
Sleep Apnea	52 (34.7%)
COPD	10 (6.7%)
CHA_2DS_2-VASc Score	
Mean ± Standard Deviation	2.2 ± 1.4
Median	2
25th percentile – 75th percentile	1 – 3
Minimum – Maximum	0 – 6
≥ 2	101 (67.3%)
Not reported (%)	6 (4.0%)
Baseline Medications	
Beta-blocker	40 (26.7%)
Calcium-channel blocker	32 (21.3%)
Anticoagulant	134 (89.3%)
Aspirin	7 (4.7%)
Class I/III AAD	**91 (60.7%)**
Amiodarone	32 (21.3%)
Dofetilide	4 (2.7%)
Dronedarone	7 (4.7%)
Flecainide	24 (16.0%)
Propafenone	12 (8.0%)
Sotalol	16 (10.7%)
AFEQT Summary Score	
Mean ± Standard Deviation	61.1 ± 20.8
Not reported (%)	2 (1.3%)
SF-12 Physical Component Summary Score	
Mean ± Standard Deviation	43.5 ± 10.5
Not reported (%)	2 (1.3%)
SF-12 Mental Component Summary Score	
Mean ± Standard Deviation	48.5 ± 10.1
Not reported (%)	2 (1.3%)

[a] CIP Versions 1-5 entrance criteria required subjects to have a BMI ≤ 40. CIP Version 6 removed the exclusion criteria of > 40 BMI. Seven (7) subjects were enrolled under CIP v6 with BMI > 40.

7.5 Index Ablation Procedure

Table 48 summarizes the types of ablations performed during the index ablation procedure and the device(s) used. The study protocol required ablation of the cavotricuspid isthmus (CTI) for subjects with a history of typical AFL or inducible CTI-dependent AFL. Additionally, other right atrial ablations were allowed during the index procedure if clinically necessary.

Table 48. Ablations Performed during Index Procedure

Procedural Characteristics	**Subjects with Index Procedures (N = 150)**
Cryoballoon Pulmonary Vein Ablation	**150 (100.0%)**
23 mm balloon size	1 (0.7%)
28 mm balloon size	141 (94.0%)
23 and 28 mm balloon size	8 (5.3%)
Focal Ablation (Freezor MAX) on Pulmonary Vein	**3 (2.0%)**
Focal Ablation (Radiofrequency [RF]) on Pulmonary Vein	**0 (0.0%)**
Cavo-tricuspid Isthmus (CTI) Ablation	**40 (26.7%)**
Focal Cryo	0 (0.0%)
Focal RF	40 (26.7%)
Other Right Atrial Ablations	**3[a] (2.0%)**

[a] Two were atrial tachycardia ablations and one was AVNRT ablation

7.6 Post-ablation AAD therapy

The study protocol recommended discontinuation of Class I and III antiarrhythmic drugs by the end of the 90-day post-procedure blanking period. However, subjects were allowed to remain on Class I or III antiarrhythmic medications at the historic maximum ineffective dose (on prior to the ablation procedure) after the 90-day post-procedure blanking period.

As indicated in *Table 49*, the majority of the 150 treated subjects were on a Class I or III AAD at discharge and about half of the subjects remained on a Class I or III AAD at 3 months post-ablation. More than 30% of the subjects were prescribed a Class I or III AAD at 6 months and 12 months post procedure.

Table 49. Class I/III AAD use at discharge, 3, 6, and 12 months post procedure

Class I/III AAD[a]	N (%) on AAD at Discharge (n = 150)	N (%) on AAD at 3 Months (n=147)	N (%) on AAD at 6 Months (n=142)	N (%) on AAD at 12 Months (n=133)
Number of Subjects on AAD	98 (65.3%)	67 (45.6%)	49 (34.5%)	40 (30.1%)
Amiodarone	33 (22.0%)	18 (12.2%)	13 (9.2%)	12 (9.0%)
Dofetilide	5 (3.3%)	4 (2.7%)	3 (2.1%)	3 (2.3%)
Dronedarone	7 (4.7%)	5 (3.3%)	5 (3.5%)	5 (3.8%)
Flecainide	30 (20.0%)	17 (11.5%)	9 (6.3%)	5 (3.8%)
Propafenone	12 (8.0%)	9 (6.1%)	7 (4.9%)	6 (4.5%)
Sotalol	17 (11.3%)	16 (10.8%)	14 (9.8%)	11 (8.3%)

[a] In this analysis, at months m = 3, 6, and 12, subjects with exit dates prior to month m (or in rare cases, with unknown AAD status) are not included.

7.7 Repeat cryoballoon ablation during the blanking period

The study allowed the following repeat ablations during the 90-day post-procedure blanking period: pulmonary vein isolation ablation using Arctic Front Advance, and ablation in the right atrium.

As shown in *Table 50*, 7 (4.7%) subjects in the mITT cohort underwent a repeat ablation procedure within the 90-day blanking period. Of these 7 subjects, 2 were reported as treatment failures, one due to cryoablation in the left atrium outside of the pulmonary veins and one due to RF ablation of the PV.

Table 50. Details of Repeat Ablations within 90-Day Blanking Period

Subject	Catheter Type	Type of Ablation	Days from Index Procedure	Number of PVs Re-treated	Primary Effectiveness Endpoint Failure?
M100001005	Cryoballoon	PVI	74	4	No
M100001010	Cryoballoon	Left atrial roof line/Left atrial posterior wall	82	0	Yes
M100001011	Cryoballoon	PVI	90	4	No
M100011004	Focal RF	Cavotricuspid Isthmus (CTI line)	42	0	No
M100011007	Focal RF	Cavotricuspid Isthmus (CTI line)	48	0	No
M134170002	Focal RF	Cavotricuspid Isthmus (CTI line)	14	0	No
M200001002	Focal RF	PVI	89	1	Yes

7.8 Rhythm monitoring compliance

Table 51 displays data on compliance to the required 12-lead ECG and 24-Hour Holter during follow-up. A total of 408 completed visits required ECGs to be performed in mITT subjects, of which 408 (100%) were completed. The STOP Persistent AF protocol did not require Holter monitoring at the 3-month or unscheduled visits; 233 of the 264 required Holter were completed, resulting in an overall compliance rate of 88.3%.

Table 51. Rhythm monitoring compliance in mITT subjects

Visit Name	Completed Visits	12-lead ECG Completion	24-Hour Holter Completion
3-Month Follow-Up	144	144 (100.0%)	24-Hour Holter not required
6-Month Follow-Up	134	134 (100.0%)	121 (90.3%)
12-Month Follow-Up	130	130 (100.0%)	112 (86.2%)
Total	408	408 (100.0%)	233 (88.3%)

Figure 5 displays compliance to the required weekly transmissions of trans-telephonic monitoring (TTM). Study subjects were instructed to perform trans-telephonic monitoring (TTM) weekly, beginning one week after the 3-month visit. Subjects were followed for a total of 5225 weeks post 3 months, of which a total of 3772 weekly transmissions were received, resulting in an overall compliance rate of 72.2%, as shown in *Table 52*.

Figure 5. Weekly Trans-Telephonic Monitoring (TTM) Compliance

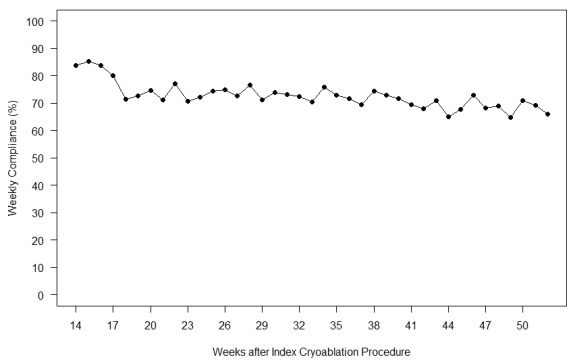


Table 52. Overall TTM Compliance

	Overall TTM Compliance
Number of total weeks of follow up[a],[b]	5225
Number of weeks with reported TTM	3772
Overall TTM compliance	72.2%

[a] TTM transmissions are expected starting 7 days after the 3-month visit. If subject missed 3-month visit, TTM compliance calculations assume transmissions after day 121 (end of 3 month visit window).

[b] This includes eligible weeks between 13- and 52-weeks post ablation, so the maximum number of expected weeks per subject is 40. Week 13 post ablation is not included in the plot, as only subjects receiving TTM equipment at out-of-window early 3-month follow-up visits had expected TTM transmissions in week 13.

In addition to the required weekly TTM transmissions and required study visits, subjects were trained to complete TTM transmissions upon symptoms. In total, an additional 509 TTMs were reported. Also, when a subject attended the clinic for an unscheduled visit, the study required an Unscheduled Visit CRF to be completed which included collection of an ECG. A total of 34 ECG's from unscheduled visits were reported over the duration of the study.

7.9 Results

7.9.1 Safety results

7.9.1.1 Primary Safety Endpoint

Per study protocol, the primary safety analysis included all 150 subjects in whom an Arctic Front Advance Catheter was inserted into their vasculature.

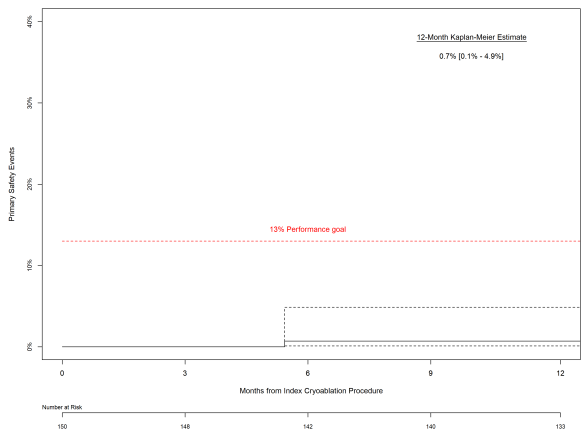
One (1) of the 150 mITT subjects experienced a primary safety event, which was a procedure-related cardiac perforation that occurred during a planned RF repeat ablation procedure . Primary safety events are listed in *Table 53*. There were no primary safety events related to the catheters.

Table 53. Primary Safety Event details: mITT subjects

Primary Safety Event	Number of Subjects with Event (%) Total subjects N = 150
Transient ischemic attack (within 7 days of ablation procedure)	0 (0.0%)
Cerebrovascular accident (within 7 days of ablation procedure)	0 (0.0%)
Major bleeding that requires transfusion (within 7 days of ablation procedure)	0 (0.0%)
Cardiac perforation, tamponade or pericardial effusion (within 7 days of ablation procedure)	1 (0.7%)
Pulmonary vein stenosis (>75% reduction within 12 months of ablation procedure)	0 (0.0%)
Myocardial infarction (within 7 days of ablation procedure)	0 (0.0%)
Phrenic nerve injury (unresolved at 12 months)	0 (0.0%)
Atrio-esophageal fistula (within 12 months of ablation procedure)	0 (0.0%)
Death (within 7 days of ablation procedure)	0 (0.0%)

As depicted in *Figure 6* below, the Kaplan-Meier estimate of rate of primary safety events at 12 months was 0.7% [95% CI: 0.1% - 4.9%]. Because the upper 95% confidence bound (4.9%) is below the predefined performance goal (13%), the primary safety endpoint was met.

Figure 6. Primary Safety at 12 Months



7.9.1.2 Summary of All Adverse Events

Adverse events occurring during the study were continuously monitored and collected. All adverse events in all enrolled subjects are summarized below. There were no Unanticipated Adverse Device Effects or deaths reported in the STOP Persistent AF study. A total of 201 adverse events were reported during the study of which 198 adverse events occurred during or after the index ablation procedure and 3 occurred prior to index ablation procedure (see details in *Table 54*). All events were adjudicated by the Clinical Events Committee (CEC). For adverse event analysis, the CEC determination of seriousness and relatedness status was used.

Table 54. Adverse Events Occurring Prior to Ablation Procedure

Adverse Events	Number of Events (Number of Subjects, % of Subjects) Total subjects: N=169
Electrocardiogram ST segment elevation	1 (1, 0.6%)
Hypotension	1 (1, 0.6%)
Lung neoplasm malignant	1 (1, 0.6%)
Total Adverse Events Prior to Procedure	**3 (3, 1.8%)**

There were 150 subjects who underwent cryoablation in this study. AEs in the 150 treated subjects are summarized below. A summary of the relatedness to the procedure or to any component of the system (including the balloon cryocatheter, focal cryocatheter, FlexCath sheath, CryoConsole, manual retraction kit, or other) and seriousness is provided in *Table 55*.

Table 55. Summary of Adverse Events Reported During or After Index Ablation Procedure

Denominator: mITT Cohort N= 150 **Number of Events (Number of Subjects, % of Subjects)**		
Adverse Event Classifications	**All Adverse Events**	**Serious Adverse Events**
Total Adverse Events	**198 (88, 58.7%)**	**43 (27, 18.0%)**
Relationship to Index CryoAblation Procedure		
Not related	154 (77, 51.3%)	36 (24, 16.0%)
Related	39 (32, 21.3%)	5 (4, 2.7%)
Unknown	0 (0, 0.0%)	0 (0, 0.0%)
Relationship to Repeat CryoAblation Procedure (Number of Repeat CryoAblation procedures = 3)		
Not related	2 (2, 66.7%)	0 (0, 0.0%)
Related	3 (2, 66.7%)	2 (2, 66.7%)
Unknown	0 (0, 0.0%)	0 (0, 0.0%)
Relationship to CryoAblation System		
Not related	172 (82, 54.7%)	40 (25, 16.7%)
Related	25 (22, 14.7%)	3 (3, 2.0%)
- Arctic Front Advance	19 (17, 11.3%)	2 (2, 1.3%)

Table 55. Summary of Adverse Events Reported During or After Index Ablation Procedure (continued)

Denominator: mITT Cohort N= 150		
Number of Events (Number of Subjects, % of Subjects)		
- Freezor MAX	0 (0, 0.0%)	0 (0, 0.0%)
- Achieve Advance Mapping Catheter	0 (0, 0.0%)	0 (0, 0.0%)
- Achieve Mapping Catheter	0 (0, 0.0%)	0 (0, 0.0%)
- FlexCath Advance Sheath	6 (6, 4.0%)	1 (1, 0.7%)
- Manual Retraction Kit	0 (0, 0.0%)	0 (0, 0.0%)
Unknown	1 (1, 0.7%)	0 (0, 0.0%)
Relationship to CardioInsight Mapping System		
Not related	198 (88, 58.7%)	43 (27, 18.0%)
Related	0 (0, 0.0%)	0 (0, 0.0%)
Unknown	0 (0, 0.0%)	0 (0, 0.0%)
Relationship to Other Devices		
Not related	196 (87, 58.0%)	42 (27, 18.0%)
Related	2 (2, 1.3%)	1 (1, 0.7%)
Unknown	0 (0, 0.0%)	0 (0, 0.0%)
Relationship to Other Procedure		
Not related	197 (88, 58.7%)	42 (27, 18.0%)
Related	1[a] (1, 0.7%)	1 (1, 0.7%)
Unknown	0 (0, 0.0%)	0 (0, 0.0%)

[a] The single adverse event related to other procedure was a cardiac perforation that occurred during transseptal puncture. This adverse event was classified by the CEC as related to a repeat RF ablation procedure and was determined to meet the criteria for the primary safety endpoint.

Of the 198 adverse events that occurred during or after the ablation procedure, 43 were classified as serious adverse events (SAEs); 25 adjudicated as related to the cryoablation system, of which 3 were SAEs; and 42 adjudicated as related to a cryoablation procedure, of which 7 were SAEs.

The three (3) cryoablation system-related SAEs were the following:

- Atrial tachycardia (n = 1);
- Pericarditis (n = 1);
- Pseudoaneurysm requiring thrombin injection (n = 1).

The seven (7) cryoablation procedure-related SAEs were the following:

- Atrial tachycardia (n = 1);
- Pericarditis (n = 1);
- Heart failure (n = 1);
- Postoperative ileus (n = 1);
- Respiratory failure (n = 1);
- Urinary tract infection (n = 1);
- Pseudoaneurysm requiring thrombin injection (n = 1).

Table 56 below summarizes all 198 adverse events that occurred during or after the ablation procedure.

Table 56. Relatedness of Adverse Events Occurring During or After Ablation Procedure

Denominator: mITT Cohort (N = 150)						
Number of Events (Number of Subjects, % of Subjects)						
Adverse Events (MedDRA Preferred Term)	**Total Events**	**Serious Adverse Events**	**Cryoablation System Related**	**Serious Cryoablation System Related**	**Cryoablation Procedure Related**	**Serious Cryoablation Procedure Related**
Total	**198 (88, 58.7%)**	**43 (27, 18.0%)**	**25 (22, 14.7%)**	**3 (3, 2.0%)**	**42 (34, 22.7%)**	**7 (6, 4.0%)**
Atrial fibrillation	70 (46, 30.7%)	9 (8, 5.3%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Atrial flutter	24 (20, 13.3%)	(0, 0.0%)	5 (5, 3.3%)	(0, 0.0%)	5 (5, 3.3%)	0 (0, 0.0%)
Chest discomfort	8 (7, 4.7%)	0 (0, 0.0%)	5 (5, 3.3%)	0 (0, 0.0%)	6 (6, 4.0%)	0 (0, 0.0%)
Hypertension	6 (6, 4.0%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Dyspnoea	4 (4, 2.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Palpitations	4 (4, 2.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Hypotension	3 (3, 2.0%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)	2 (2, 1.3%)	0 (0, 0.0%)
Oropharyngeal pain	3 (3, 2.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	3 (3, 2.0%)	0 (0, 0.0%)
Phrenic nerve paralysis	3 (3, 2.0%)[a]	0 (0, 0.0%)	3 (3, 2.0%)	0 (0, 0.0%)	3 (3, 2.0%)	0 (0, 0.0%)
Anaemia	2 (2, 1.3%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Atrial tachycardia	2 (2, 1.3%)	1 (1, 0.7%)	1 (1, 0.7%)	1 (1, 0.7%)	1 (1, 0.7%)	1 (1, 0.7%)
Cardiac failure	2 (2, 1.3%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Cardiac failure congestive	2 (2, 1.3%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Cough	2 (2, 1.3%)	0 (0, 0.0%)	2 (2, 1.3%)	0 (0, 0.0%)	2 (2, 1.3%)	0 (0, 0.0%)
Non-cardiac chest pain	2 (2, 1.3%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Pericarditis	2 (2, 1.3%)	1 (1, 0.7%)	2 (2, 1.3%)	1 (1, 0.7%)	2 (2, 1.3%)	1 (1, 0.7%)
Pneumonia	2 (2, 1.3%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)
Vascular access site haematoma	2 (2, 1.3%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)	2 (2, 1.3%)	0 (0, 0.0%)
Ventricular tachycardia	2 (2, 1.3%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Acute kidney injury	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Acute left ventricular failure	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Acute myocardial infarction	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Angina pectoris	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Aortic perforation	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Arrhythmia supraventricular	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Asthma	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)

Table 56. Relatedness of Adverse Events Occurring During or After Ablation Procedure (continued)

Denominator: mITT Cohort (N = 150) Number of Events (Number of Subjects, % of Subjects)						
Atrioventricular block first degree	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Bacterial sepsis	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Breast cancer	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Bronchitis	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Cardiac failure acute	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	1 (1, 0.7%)	1 (1, 0.7%)
Chest pain	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Cholecystitis chronic	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Conjunctivitis viral	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Coronary artery disease	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Crohn's disease	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Diverticulitis	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Electro-cardiogram QT prolonged	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Epistaxis	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Fluid retention	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Gastro-esophageal reflux disease	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Haemoptysis	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)
Heart rate irregular	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Hemiparesis	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Hyponatraemia	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Incision site haemorrhage	1 (1, 0.7%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)
Labyrinthitis	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Musculoskeletal discomfort	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)
Neck mass	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Odynophagia	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Osteoarthritis	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Pneumothorax	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Postoperative hypotension	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)
Postoperative ileus	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	1 (1, 0.7%)	1 (1, 0.7%)
Procedural hypertension	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)
Puncture site pain	1 (1, 0.7%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)
Respiratory failure	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	1 (1, 0.7%)	1 (1, 0.7%)
Sinus bradycardia	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Sinus tachycardia	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Squamous cell carcinoma of the tongue	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Supraventricular extrasystoles	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Supraventricular tachycardia	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Systolic hypertension	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Transient ischaemic attack	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Ureteric injury	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Urinary tract infection	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	1 (1, 0.7%)	1 (1, 0.7%)
Vaginal haemorrhage	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)
Vascular access site haemorrhage	1 (1, 0.7%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)
Vascular access site pain	1 (1, 0.7%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)
Vascular pseudoaneurysm	1 (1, 0.7%)	1 (1, 0.7%)	1 (1, 0.7%)	1 (1, 0.7%)	1 (1, 0.7%)	1 (1, 0.7%)
Ventricular extrasystoles	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Vomiting	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)

[a] Three (3) phrenic nerve injuries were reported. Two of these resolved prior to discharge from the index ablation. The third resolved after 6 months but prior to the subject's exit from the study.

7.9.1.3 Phrenic Nerve Injury

Phrenic nerve injury resulting in diaphragmatic paralysis occurred in three (3) of 150 subjects (2%) who underwent a cryoballoon ablation procedure. None of the 3 occurrences of diaphragmatic paralysis was classified by the CEC as a SAE. Two of these occurrences resolved prior to discharge from the index ablation. The third persisted for at least 6 months and its recovery was not confirmed on chest x-ray until 15 months post ablation prior to subject's exit from the study. Since this occurrence of diaphragmatic paralysis was not classified as a SAE, the adverse event did not count towards the primary safety endpoint.

7.9.2 Effectiveness results

7.9.2.1 Primary Effectiveness Endpoint

Per study protocol, the primary effectiveness analysis was based on primary effectiveness success using the mITT cohort as the primary analysis population.

Of the 150 mITT subjects, 69 reported at least one primary effectiveness failure through 12 months of follow-up. The distribution of first primary effectiveness failure events observed in the 69 subjects are as follows:

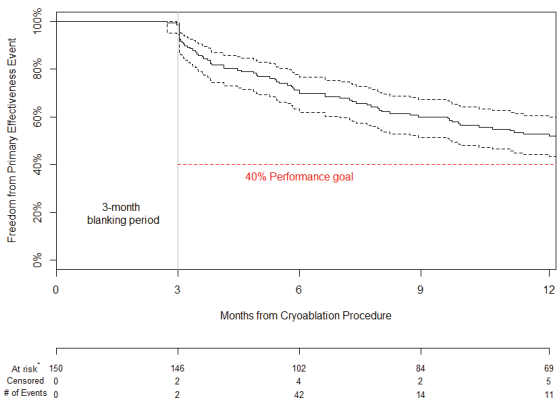
- 0 with acute procedure failures
- 2 with additional interventions in the left atrium within the 90-day blanking period

- 57 with AF/AT/AFL post the blanking period
  - 44 atrial fibrillation (AF)
  - 9 atrial flutter (AFL)
  - 1 atrial fibrillation and atrial flutter
  - 3 atrial tachycardia (AT)
- 10 AAD dose higher than pre-ablation maximum

The rate of freedom from primary effectiveness failure at 12 months was estimated to be 52.1% [95% CI: 43.6 - 59.9%] using the Kaplan-Meier method.

Figure 7 displays the Kaplan-Meier curve for freedom from primary effectiveness failure for mITT subjects (n=150) through 12 months post procedure. The solid line is the Kaplan-Meier estimate, and the dashed lines are the 95% confidence interval. Because the lower bound of 95% confidence interval was greater than the predefined performance goal of 40%, the primary effectiveness endpoint was met.

Figure 7. Freedom from Primary Effectiveness Failure at 12 Months



* The number at risk, number censored, and number of events are included per Kaplan-Meier analysis methods: at risk equals the number of patients at risk up to months 3, 6, 9, and 12; number censored equals the number of patients censored up to months 3, 6, 9, and 12; number of events equals the number of events through the end of the intervals.

Class I/III AAD use in subjects without a primary effectiveness failure event

Data on Class I and III AAD use was collected at each follow-up visit. The study allowed subjects to be remained on a Class I or III AAD at the historic maximum ineffective dose after the blanking period. Per study protocol, such subjects were not classified as primary effectiveness failures for taking a Class I or III AAD during the 9-month effectiveness evaluation period (days 91-365 post procedure).

Among the 150 mITT subjects, 69 were classified as primary effectiveness failures and 81 had not experienced a primary effectiveness failure event. As indicated in *Table 57*, approximately 40% of the subjects without a primary effectiveness failure event remained on a Class I or III AAD at 3 months post procedure. The proportion of the subjects without a primary effectiveness failure event prescribed a previously ineffective Class I or III AAD decreased during the course of 9-month effectiveness evaluation period to approximately 24% at 12 months post procedure.

Table 57. Class I/III AAD use in subjects without a primary effectiveness failure event

	Subjects without a Primary Effectiveness Failure Event (n=81)				
Class I and III AADs[a]	**N (%) on AAD at Baseline (n = 81)**	**N (%) on AAD at Discharge[b] (n = 80)**	**N (%) on AAD at 3 Months[c] (n = 78)**	**N (%) on AAD at 6 Months (n = 74)**	**N (%) on AAD at 12 Months (n = 67)**
Number of Subjects on AAD[d]	47 (58.0%)	50 (62.5%)	30 (38.5%)	21 (28.4%)	16 (23.9%)
Amiodarone	18 (22.2%)	18 (22.5%)	9 (11.5%)	6 (8.1%)	5 (7.5%)
Dofetilide	3 (3.7%)	3 (3.7%)	1 (1.3%)	0	0
Dronedarone	4 (4.9%)	4 (4.9%)	2 (2.5%)	2 (2.7%)	2 (3.0%)
Flecainide	15 (18.5%)	18 (22.2%)	7 (8.9%)	3 (4.0%)	1 (1.5%)
Propafenone	6 (7.4%)	6 (7.4%)	6 (7.6%)	6 (8.0%)	4 (6.0%)
Sotalol	5 (6.2%)	6 (7.4%)	6 (7.6%)	5 (6.7%)	5 (7.5%)

[a] In this analysis, at months m = 3, 6, and 12, subjects with exit dates prior to month m (or in rare cases, with unknown AAD status) are not included.

[b] One subject had no date specified for the discontinuation of amiodarone at a dose less than the pre-ablation maximum; therefore, the status at hospital discharge could not be determined.

[c] Two subjects exited the study during the blanking period, and one subject had no date specified for the discontinuation of amiodarone at a dose less than the pre-ablation maximum; therefore, the status at day 90 for these subjects could not be determined.

[d] Medications and medication changes were captured on a Medication Log CRF. Centers were instructed to update a Medication Log with prescription changes. For analysis, the time at 3 months was defined as day 90, similarly 6 months and 12 months were defined as day 180 and day 365. Prescription data are through study exit.

7.9.2.2 Acute Procedural Success

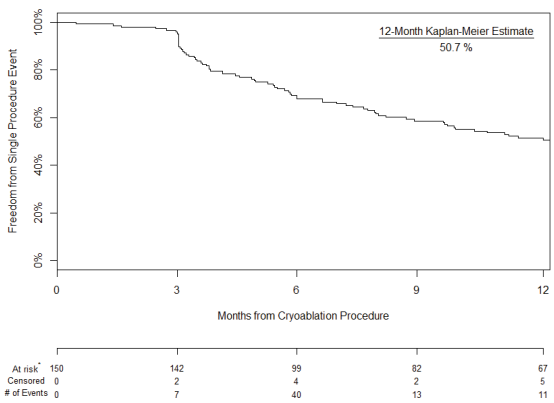
An analysis was performed to evaluate acute procedural success for the mITT cohort.

All 150 mITT subjects experienced acute procedural success (100%) with all pulmonary veins isolated using the study devices at index ablation. A Freezor MAX CryoAblation Catheter was utilized for 4 (0.7%) of 588 pulmonary veins in 3 (2%) of 150 mITT subjects to complete PV isolation.

7.9.2.3 12-month Single Procedural Success

Seven (7) subjects had a repeat ablation within the 90-day blanking period. When these repeat ablations were counted as effectiveness failures, the single procedure success rate was estimated to be 50.7% based on the Kaplan-Meier curve shown in *Figure 8* below.

Figure 8. Single Procedure Freedom from Primary Effectiveness Failure at 12 Months



* The number at risk, number censored, and number of events are included per Kaplan-Meier analysis methods: at risk equals the number of patients at risk up to months 3, 6, 9, and 12; number censored equals the number of patients censored up to months 3, 6, 9, and 12; number of events equals the number of events through the end of the intervals.

7.9.2.4 Treatment Success in subjects off Class I and III AADs

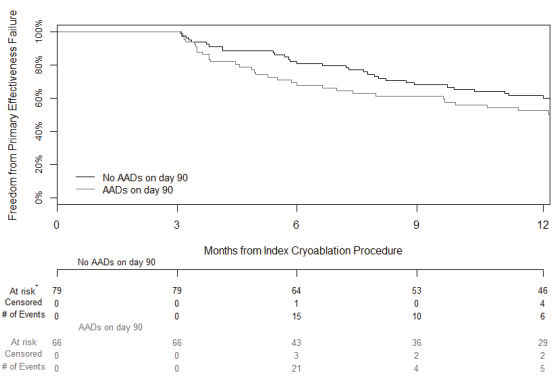
This endpoint compared treatment success in subjects on vs. those off Class I and Class III AADs on day 90 post procedure.

Of the 150 mITT subjects, 145 were included in the analysis. Five (5) subjects were not included due to:

- Study exit prior to 90 days (n = 2);
- primary effectiveness failure prior to day 90 (n =2);
- unknown Class I/III AAD use status on day 90 post procedure (n = 1).

Figure 9 and *Table 58* display the results of primary effectiveness by Class I/III AAD use on day 90 post procedure. Of the 145 subjects included in the analysis, 79 were not prescribed a Class I or III AAD, and 66 were prescribed a Class I or III AAD on day 90. As shown in *Table 58*, the primary effectiveness success rate in subjects who were taking a Class I or III AAD on day 90 post-index ablation was approximately 10% lower than that in those who were not.

Figure 9. Freedom from Primary Effectiveness Failure at 12 Months by Class I/III AAD use on day 90 Post Procedure



* The number at risk, number censored, and number of events are included per Kaplan-Meier analysis methods: at risk equals the number of patients at risk up to months 3, 6, 9, and 12; number censored equals the number of patients censored up to months 3, 6, 9, and 12; number of events equals the number of events through the end of the intervals.

Table 58. Primary Effectiveness Success at 12 Months by Class I/III AAD use on Day 90 Post Procedure

Subgroup	N	Kaplan-Meier Rate
On AAD on Day 90	66	50.4%
Off AAD on Day 90	79	60.2%

7.9.3 Additional results

7.9.3.1 Secondary endpoint (Improvement in Quality of life)

7.9.3.2 AFEQT score

Of the 150 mITT subjects, 126 subjects fully completed a questionnaire at both baseline and 12-month visit. As shown in *Table 59*, the difference in AFEQT score between baseline and 12 months was a statistically significant (<.0001). The average improvement in AFEQT score at 12 months post-index procedure was 26.7 [95% CI: 22.7, 30.8].

Table 59. AFEQT Results through 12 Months

N	Baseline	12 Months Visit	Difference (95% CI)	Unadjusted p-value
126	62.4 ± 20.8	89.1 ± 14.3	26.7 (95% CI: 22.7, 30.8)	<.0001

Figure 10 depicts the change in AFEQT score from baseline through 6 and 12 months. This figure includes all data, not just for the subjects with both baseline and 12 months data available. Therefore, the number of patients included for the baseline AFEQT score was slightly different from that in *Table 59*, however the results were consistent with the paired analysis in *Table 59*. The results showed that the AFEQT score improved at 6 months and the improvement persisted at 12 months post ablation.

Figure 10. AFEQT Results by Visit

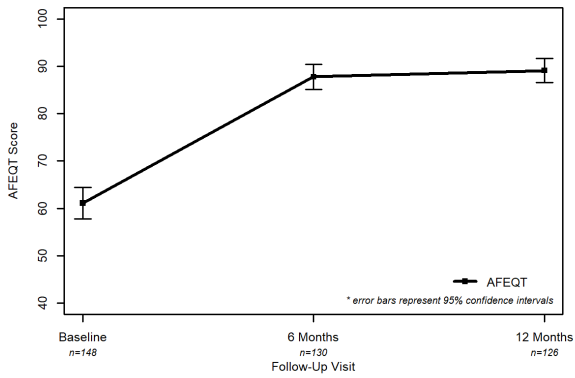


Table 60. AFEQT Results by Visit

Visit	N	Mean ± SD
Baseline	148	61.1 ± 20.8
6 Months Follow-up	130	87.8 ± 15.4
12 Months Follow-up	126	89.1 ± 14.3

7.9.3.3 SF-12 Mental and Physical Scores

Of the 150 mITT subjects, 127 subjects fully completed a SF-12 questionnaire at both baseline and 12-month visit. As shown in *Table 61*, for both the physical and mental components, there was a statistically significant (<.0001) improvement at 12 months post-procedure. The average improvement in SF-12 physical component score was 5.2 [95% CI: 3.7, 6.7]. The average improvement in SF-12 mental component score was 5.1 [95% CI: 3.2, 6.9].

Table 61. SF-12 Results through 12 Months

SF-12 Component	N	Baseline	12 Months Visit	Difference (95% CI)	p-value
SF-12 Physical Component	127	44.0 ± 9.5	49.1 ± 8.3	5.2 (3.7 - 6.7)	<.0001
SF-12 Mental Component	127	49.1 ± 10.1	54.2 ± 7.7	5.1 (3.2 - 6.9)	<.0001

Figure 11 depicts the change in SF-12 scores from baseline through 6 and 12 months. This figure includes all data, not just for the subjects with both baseline and 12 months data available. Thus, there are slight differences in the baseline averages that arise from including the extra subjects. The results showed that both scores increased at 6 months and the improvements persisted at 12 months post ablation.

Figure 11. SF-12 Results through 12 Months

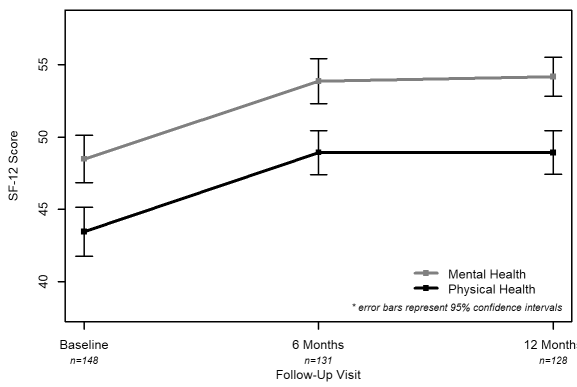


Table 62. SF-12 Summary Scores by Visit

Visit	N	SF-12 Physical Component Mean ± SD	SF-12 Mental Component Mean ± SD
Baseline	148	43.5 ± 10.5	48.5 ± 10.1
6 Months	131	48.9 ± 8.8	53.9 ± 9.0
12 Months	128	48.9 ± 8.6	54.2 ± 7.7

A Hommel multiple testing procedure was utilized to maintain an overall type I error rate of 0.025 for the three hypotheses tested for the secondary endpoints. The three hypotheses tested were change in AFEQT, change in SF-12 mental component, and change in SF-12 physical component. The largest p-value among three tests was < 0.025 (all p-values were < 0.0001). Therefore, according to Hommel multiple testing procedure, all three quality of life endpoints were met.

7.9.3.4 Procedure Measurements

All 150 mITT subjects underwent pulmonary vein ablation with a Cryoballoon. The following data were derived from index procedures only. Summary statistics for procedure times are displayed in *Table 63*.

It is noted that in 8 of 150 index procedures, the last sheath removal occurred in the recovery room at an average of 62.4 minutes (range: 19 – 212 minutes) after the subjects had left the electrophysiology room per physician discretion. Total procedure time and left atrial dwell time calculations ended at the time of last sheath removal.

Table 63. Procedure Measurements

	Subjects with Index Procedures (N = 150)
Total Procedure Time (mins)	
Mean ± Standard Deviation	122 ± 47
Median	113
25th Percentile - 75th Percentile	88 - 146
Minimum - Maximum	48 - 357
Not reported (%)	1 (1%)
Left Atrial Dwell Time (mins)	
Mean ± Standard Deviation	103 ± 42
Median	96

Table 63. Procedure Measurements (continued)

	Subjects with Index Procedures (N = 150)
25th Percentile - 75th Percentile	75 - 117
Minimum - Maximum	43 - 346
Not reported (%)	1 (1%)
Study Device Left Atrial Dwell Time (mins)	
Mean ± Standard Deviation	67 ± 25
Median	65
25th Percentile - 75th Percentile	49 - 81
Minimum - Maximum	16 - 164
Not reported (%)	1 (1%)
Total Fluoroscopy Time (mins)	
Mean ± Standard Deviation	17.0 ± 13.1
Median	14.7
25th Percentile - 75th Percentile	6.8 - 23.9
Minimum - Maximum	0.1 - 65.9
Not reported (%)	3 (2.0%)
Application Duration (mins)	
Mean ± Standard Deviation	24.9 ± 8.0
Median	24.0
25th Percentile - 75th Percentile	19.2 - 28.5
Minimum - Maximum	13.0 - 51.8
Not reported (%)	0 (0.0%)

7.9.3.5 Atrial Arrhythmias Present and/or Treated

Atrial arrhythmias in addition to AF present and/or treated during the index cryoablation procedure are summarized in *Table 64*. The most frequent additional atrial arrhythmia was cavo-tricuspid isthmus (CTI)-dependent atrial flutter.

Table 64. Arrhythmias in addition to AF present and/or treated during the index cryoablation procedure

Arrhythmia	Number of subjects with arrhythmia present N (%) [95% CI]	Number of subjects with arrhythmia treated N (%)
Atrioventricular nodal reentrant tachycardia (AVNRT)	1 (0.7%) [0.0 - 3.7%]	1 (100.0%)
Cavo-tricuspid isthmus (CTI)-dependent Atrial Flutter	40 (26.7%) [19.8 - 34.5%]	40 (100.0%)
Other	4 (2.7%) [0.7 - 6.7%]	2[a] (50.0%)

[a] Both were right atrial tachycardia

7.10 Study conclusions

In conclusion, the results of the STOP Persistent AF study demonstrated that there is a reasonable assurance of safety and effectiveness of the Arctic Front Advance and Freezor MAX Cardiac CryoAblation Catheters when used for the treatment of symptomatic drug refractory recurrent persistent AF of less than 6 months duration.

8 Adverse events

Potential adverse events associated with cardiac catheter cryoablation procedures include, but are not limited to, the following conditions:

- Access site complications (e.g. bruising, ecchymosis)
- Anemia
- Anxiety
- Arrhythmia (e.g. atrial flutter, bradycardia, heart block, tachycardia)
- Back pain
- Bleeding from puncture sites
- Bronchial constriction
- Bronchial fistula
- Bronchitis
- Bruising
- Cardiac tamponade
- Cardiopulmonary arrest
- Cerebral vascular accident
- Chest discomfort/pain/pressure
- Cold feeling
- Coronary artery spasm
- Cough
- Death
- Diarrhea
- Dizziness
- Embolism
- Esophageal damage (including atrio-esophageal fistula)
- Fatigue
- Fever
- Headache
- Hemoptysis
- Hypotension/hypertension
- Infection (e.g. pericarditis, sepsis, urinary)
- Lightheadedness
- Myocardial infarction
- Nausea/vomiting
- Perforation
- Pericardial effusion
- Phrenic nerve injury
- Pleural effusion
- Pneumonia
- Pneumothorax
- Pseudoaneurysm
- Pulmonary edema
- Pulmonary hemorrhage
- Pulmonary vein dissection
- Pulmonary vein stenosis
- Shivering
- Shortness of breath
- Sore throat
- Transient ischemic attack
- Vagal nerve injury (e.g. gastroparesis)
- Vasovagal reaction
- Visual changes (e.g. blurred vision)

9 Instructions for use

9.1 Connecting the Arctic Front Advance Cardiac Cryoablation Catheter

During connection of the catheter, keep the connections dry at all times. Fluid incursion may lead to system malfunction. To connect the catheter, follow these steps. (For more detailed instructions, see the *CryoConsole Operator's Manual*.)

1. Connect the auto connection box to the CryoConsole.
   Note: The ECG cable is not required for an Arctic Front Advance Cryoballoon procedure, and should not be connected to the auto connection box.
2. Connect the catheter to a sterile electrical umbilical cable and then pass the other end of the cable out of the sterile field and connect it to the auto connection box.
3. Connect the catheter to a sterile coaxial umbilical cable and then pass the other end of the cable out of the sterile field and connect it to the CryoConsole.
4. Enable vacuum on CryoConsole.

9.2 Cryoablation

To use the catheter for a cryoablation procedure, follow these steps. (For more detailed instructions, see the *CryoConsole Operator's Manual*.)

Notes:

- Before introducing the catheter into the patient, test the deflection mechanism on the handle to ensure it is operational.
- Always use the deflection mechanism on the handle to straighten the shaft before insertion or withdrawal of the catheter.
- The Achieve family of mapping catheters is compatible for use with the Medtronic Arctic Front Advance Cryoablation Catheter and may be used to support and position the catheter.

1. Using aseptic technique, create a vascular access with an appropriate introducer. Obtain left atrial transseptal access using a transseptal sheath, its dilator, and needle.
   - Place standard diagnostic pacing catheters.
   - Visualize left atrial anatomy to help select a balloon size. Select balloon size.
   - Selection of balloon size should be based on pulmonary vein (PV) diameter and shape, the surrounding anatomy, and desired position of the balloon outside the tubular portion of the PV. PV diameter ranges are recommended as follows:

     23 mm balloon: 10-21 mm

     28 mm balloon: 16-30 mm
2. Remove the transseptal sheath and dilator, leaving the guide wire positioned preferably in the left superior pulmonary vein (LSPV).
3. Advance the sheath and dilator over the wire into the left atrium.
4. Slowly remove the guide wire and dilator from the sheath.
5. Aspirate and flush the sheath.
6. Obtain a catheter. Connect the y-connector and manifold to the push button Luer.
7. Flush the guide wire lumen, ensuring there are no air bubbles in the guide wire lumen or connections.
8. Load the circular mapping catheter or guide wire into the guide wire lumen.
9. Pull the circular mapping catheter or guide wire back into the balloon catheter until it is just inside the balloon catheter tip.
10. Flush the guide wire lumen again, ensuring there are no air bubbles in the guide wire lumen or connections.
11. Retract the sleeve from the balloon onto the catheter shaft.
12. Submerge and rinse the balloon to remove trapped air bubbles.
13. Advance the sleeve back over the balloon while the balloon is still submerged.
14. Place the sleeve adjacent to the hemostasis valve of the sheath.

    Note: To avoid damaging the valve or introducing air, do not push the sleeve through the valve opening.
15. Insert the catheter into the sheath.

    Note: Follow institutional procedures to aspirate and flush the sheath.
16. Advance the balloon until the distal tip of the catheter aligns with the distal tip of the sheath using fluoroscopic guidance or other appropriate visualization techniques.
17. Advance the circular mapping catheter or guide wire to the target pulmonary vein using fluoroscopic guidance or other appropriate visualization techniques.
18. Advance the balloon over the circular mapping catheter or guide wire into the left atrium using fluoroscopic guidance or other appropriate visualization techniques.
19. Inflate the balloon in the left atrium by pressing the Start button on the CryoConsole control panel for 2 seconds.
20. Position the catheter at the ostium of the target pulmonary vein (PV) and not inside the tubular portion of the PV.
21. Verify the balloon position by injecting a mixture of 50/50 contrast/saline into the catheter guide wire lumen port or by using other appropriate techniques. Be sure to flush the guide wire lumen with saline after each contrast injection.

    Notes:
    - To improve balloon position and support, reposition the circular mapping catheter. If a stable balloon position cannot be obtained, exchange the circular mapping catheter for a guide wire.
    - Before exchanging the circular mapping catheter for a guide wire, retract the catheter into the sheath.
    - Follow contrast labeling and institutional procedures regarding the appropriate medical strategies to minimize the risk to the patient associated with using contrast.
22. Perform the cryoablation.

    Notes:
    - During the initial ablation phase, monitor the balloon's position using appropriate visualization techniques. Moisture in the system may cause the inflated balloon to deflate and then re-inflate during the initial transition phases.
    - Set the ablation duration on the CryoConsole screen.
    - Physicians may modify the preset ablation duration based on clinical judgment.
    - The balloon's outer diameter varies from inflation to cryoablation and may cause the balloon to shift.
23. Wait for the cryoablation phase to complete (at the end of the preset duration). The balloon remains inflated and the thawing phase begins.

    Note: At any time, the ablation can be stopped by pressing the Stop Current Action button on the CryoConsole control panel or by pressing the Stop CryoAblation button on the screen.
24. During the thawing phase, observe the temperature indicator on the screen. The balloon deflates automatically when the temperature reaches 20°C.
25. Before moving the balloon, use appropriate techniques to ensure that the catheter is not adhered to tissue.
26. Determine effective ablation of the cardiac tissue by assessing electrical isolation of the pulmonary vein from the left atrium (entrance and exit block) after the cryoablation is complete.

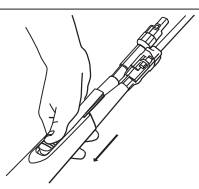
    Note: As needed, perform additional treatments by positioning the balloon differently in the same pulmonary vein.
27. Position the catheter at the ostium of the next target pulmonary vein using the sheath, circular mapping catheter, or guide wire. Return to *Step 17* and continue ablation.
28. To retract the balloon into the sheath, perform the following steps:

    Note: Ensure that the distal tip of the catheter is free to move to its maximum length.
    a. Use the deflection mechanism on the sheath handle to straighten the sheath. Use the deflection mechanism on the catheter handle to straighten the catheter.
    b. Inflate the balloon.
    c. Perform the following two steps simultaneously:

       Advance the blue push button on the catheter handle, as shown in *Figure 12*. This causes the balloon to extend to maximum length and wrap tightly.

       Deflate the balloon by pressing the Stop Current Action button on the CryoConsole control panel, or by selecting the Deflate Balloon option on the screen.
    d. Retract the catheter into the sheath.

    Figure 12. Catheter handle



29. Remove the catheter from the patient.
30. After the procedure, follow the instructions to "Shut down the system" in the *CryoConsole Operator's Manual*. Follow the prompts to close the refrigerant tank and replace the cap on the coaxial port. Confirm these actions when prompted by the CryoConsole.

10 Specifications

Catheter shaft size	3.5 mm (10.5 Fr; 0.14 in)
Tip outer diameter	3 mm (9 Fr; 0.12 in)
Recommended introducer sheath	compatible Medtronic 12 Fr inner diameter sheath
Inner diameter of guide wire lumen	1.27 mm (0.05 in) nominal
Inflated balloon diameter	2AF234 – 23 mm (0.91 in) 2AF284 – 28 mm (1.10 in)
Effective length (with balloon inflated)	95.0 ±2.0 cm (37.40 ±0.80 in)
Number of thermocouples	1
Environmental parameters	
Storage temperature	15°C to 30°C (59°F to 86°F)
Transit temperature	–35°C to 45°C (–31°F to 113°F); up to 85% relative humidity (non-condensing)
Operation	15°C to 30°C (59°F to 86°F) at altitudes less than 2400 m (8000 feet) above sea level

11 Medtronic limited warranty

For complete warranty information, see the accompanying limited warranty document.

12 Service

Medtronic employs highly trained representatives and engineers located throughout the world to serve you and, upon request, to provide training to qualified hospital personnel in the use of Medtronic products. Medtronic also maintains a professional staff to provide technical consultation to product users. For more information, contact your local Medtronic representative, or call or write Medtronic at the appropriate telephone number or address listed on the back cover.

Medtronic

Medtronic, Inc.
710 Medtronic Parkway
Minneapolis, MN 55432
USA
www.medtronic.com
+1 763 514 4000

Medtronic USA, Inc.
Toll-free in the USA (24-hour technical consultation for physicians and medical professionals)
Bradycardia: +1 800 505 4636
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Technical manuals
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2020-07-16

M810596A001

Medtronic

Arctic Front Advance Pro™ AFAPRO23, AFAPRO28

Cardiac Cryoablation Catheter

Technical Manual

Caution: Federal law (USA) restricts this device to sale by or on the order of a physician.

Explanation of symbols

The following list of symbols and abbreviations applies to various products. Refer to the package labels to see which symbols apply to this product.

Lot number

Reorder number

Use-by

Sterilized using ethylene oxide

Do not re-use

Do not resterilize

Do not use if package is damaged

Package contents

Cardiac Cryoablation Catheter

Consult instructions for use

Fragile, handle with care

Keep dry

Product documentation

Humidity limitation

Storage temperature

Transit temperature

Manufacturer

Authorized representative in the European Community

1 Description

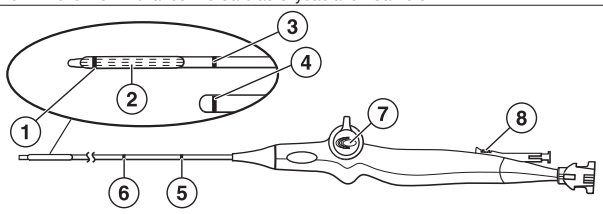
The Arctic Front Advance Pro Cardiac Cryoablation Catheter (the catheter or the Arctic Front Advance Pro Cryoballoon) is a flexible, over-the-wire balloon catheter used to ablate cardiac tissue. It is used together with a compatible Medtronic 12 Fr inner diameter sheath (the sheath), the CryoConsole, and related components. For device compatibility questions, contact Medtronic Technical Support.

The balloon reaches cryoablation temperatures when refrigerant is injected from the CryoConsole to the balloon segment. A thermocouple positioned inside the balloon provides temperature reading capability. The catheter is introduced into the vasculature by traditional, minimally invasive techniques.

There are two radiopaque markers on the catheter to confirm the position of the balloon using fluoroscopy. The proximal radiopaque marker is located approximately 10 mm (0.394 in) proximal to the balloon. The distal radiopaque marker is located at the end of the injection tube.

Note: The 12 Fr FlexCath sheath is compatible with the catheter. There is one radiopaque marker on the FlexCath sheath, located approximately 5 mm (0.197 in) proximal to the tip of the sheath (see *Figure 1*). When the catheter's proximal radiopaque marker and the FlexCath sheath's radiopaque marker are aligned, the balloon is approximately 5 mm (0.197 in) outside of the FlexCath sheath. There are two shaft markers on the proximal section of the catheter shaft to visually confirm the position of the balloon within the FlexCath sheath. When the distal marker on the shaft of the catheter is aligned with the handle of the FlexCath sheath, the balloon segment is located inside the FlexCath sheath. When the proximal marker on the shaft of the catheter is aligned with the handle of the FlexCath sheath, the balloon segment is outside the FlexCath sheath (see *Figure 1*).

Figure 1. Arctic Front Advance Pro Cardiac Cryoablation Catheter



1 Distal catheter radiopaque marker
2 Deflated balloon segment
3 Proximal catheter radiopaque marker
4 FlexCath sheath radiopaque marker
5 Proximal catheter shaft marker
6 Distal catheter shaft marker
7 Deflection mechanism
8 Blue push button

The Arctic Front Advance Pro Cardiac Cryoablation Catheter is available in 2 models, as described in the following table:

Model	Inflated balloon diameter
AFAPRO23	23 mm (0.91 in)
AFAPRO28	28 mm (1.10 in)

For details about the CryoConsole and how to use it with the catheter to perform cryoablation procedures, see the *CryoConsole Operator's Manual*.

1.1 Contents of package

The catheter is supplied sterile. The package contains the following items:

- 1 Arctic Front Advance Pro Cardiac Cryoablation Catheter
- product documentation

2 Indications for use

The Arctic Front Advance Pro Cardiac Cryoablation Catheter is indicated for the treatment of drug refractory recurrent symptomatic paroxysmal and persistent atrial fibrillation (episode duration less than 6 months).

3 Contraindications

The Arctic Front Advance Pro Cardiac Cryoablation Catheter is contraindicated as follows:

- in the ventricle because of the danger of catheter entrapment in the chordae tendineae
- in patients with active systemic infections
- in conditions where the manipulation of the catheter within the heart would be unsafe (for example, intracardiac mural thrombus)
- in patients with cryoglobulinemia
- in patients with one or more pulmonary vein stents

4 Warnings and precautions

Anticoagulation therapy – Administer appropriate levels of peri-procedural anticoagulation therapy for patients undergoing left-sided and transseptal cardiac procedures. Administer anticoagulation therapy during and post-procedure according to the institution's standards. The Arctic Front Advance Pro Cryoballoon was not studied for the safety of changes in anticoagulation therapy in patients with paroxysmal atrial fibrillation.

Balloon inflation or deflation – Do not inflate the balloon inside the sheath. Always verify with fluoroscopy or other appropriate visualization techniques that the balloon is fully outside the sheath before inflation to avoid catheter damage.

- Do not inflate the balloon while the catheter is positioned inside a pulmonary vein. Always inflate the balloon in the atrium and then position it at the pulmonary vein ostium. Inflating the balloon in the pulmonary vein may result in vascular injury.
- If the balloon cannot be inflated or deflated using the CryoConsole, have a Manual Retraction Kit on hand during the procedure. (Refer to the *CryoConsole Operator's Manual* for more detailed instructions on the Manual Retraction Kit).

Biohazard disposal – Discard all used catheters and sterile components in accordance with hospital procedures.

Cardioversion or defibrillation during ablation procedure – Disconnect the catheter's electrical connection before cardioversion or defibrillation. Failure to do so may trigger system messages indicating a need for catheter exchange.

Catheter handling – Use extreme care when manipulating the catheter. Lack of careful attention may result in injury such as perforation or tamponade.

- Do not use excessive force to advance, withdraw, or rotate the catheter, especially if resistance is encountered. Excessive force may lead to catheter damage, including kinking of the guide wire lumen within the balloon segment.
- Do not use the catheter if it is kinked, damaged, or cannot be straightened.
- Straighten the shaft before inserting or withdrawing the catheter.
- Do not at any time preshape or bend the catheter shaft or balloon segment. Bending or kinking the catheter shaft may damage internal structures and increase the risk of catheter failure. Prebending of the distal curve may damage the catheter.
- Catheter advancement should be performed using fluoroscopy or other appropriate techniques.
- Do not position the cryoballoon catheter within the tubular portion of the pulmonary vein to minimize phrenic nerve injury and pulmonary vein stenosis.

Catheter integrity – Do not use the catheter if it is kinked or damaged. If the catheter becomes kinked or damaged while in the patient, remove it and use a new catheter. Before injecting, the physician should ensure that there is no kink in the catheter.

Circular mapping catheter compatibility – Use only Medtronic circular mapping catheters compatible with the inner lumen of the Arctic Front Advance Pro Cryoballoon. Use of another mapping catheter may damage the catheter or compromise the procedure.

Contrast media – Use appropriate levels of contrast media in patients with comorbidities such as recent history of renal disease. Follow contrast labeling and institutional procedures regarding the appropriate medical strategies to minimize risk when using contrast media.

Correct guide wire or circular mapping catheter insertion and positioning – Do not advance the balloon beyond the guide wire or circular mapping catheter to reduce the risk of tissue damage.

- Ensure that the guide wire or circular mapping catheter is inserted into the catheter and through the balloon portion for adequate support during vascular access insertion. Failure to do so may result in catheter damage.

Cryoablation near prosthetic heart valves – Do not pass the catheter through a prosthetic heart valve (mechanical or tissue). The catheter may become trapped in the valve, damaging the valve and causing valvular insufficiency or premature failure of the prosthetic valve.

Cryoadhesion – Do not pull on the balloon catheter, circular mapping catheter, sheath, umbilical cables, or CryoConsole while the balloon catheter or circular mapping catheter are frozen to tissue. This may lead to tissue injury. Before moving these components, use appropriate techniques to ensure that the balloon catheter and circular mapping catheter are not adhered to tissue.

Damage to lung or tracheobronchial tree – Damage to the lung or tracheobronchial tree has been observed in some subjects who have undergone left atrial ablation with the Arctic Front family. The physician should consider appropriate medical strategies to minimize the risk of damage to the lung or tracheobronchial tree.

Do not resterilize – Do not resterilize this device for the purpose of reuse. Resterilization may compromise the structural integrity of the device or create a risk of contamination from the device that could result in patient injury, illness, or death.

Embolism risk – Introducing any catheter into the circulatory system entails the risk of air or gas embolism, which may occlude vessels and lead to tissue infarction with serious consequences. Always advance and withdraw components slowly to minimize the vacuum created and therefore minimize the risk of air embolism.

Environmental limits – Perform cryoablation procedures only within the environmental parameters. Operating outside these parameters may prevent the start or completion of a cryoablation procedure. Refer to *Chapter 10, Specifications, page 33* for environmental parameters.

Esophageal injury – Esophageal ulcerations have been observed in some subjects who have undergone left atrial ablation with the Arctic Front family. As with other forms of left atrial ablation, the physician should consider appropriate medical strategies to minimize the risk of esophageal injury.

Fluid incursion – Do not expose the catheter handle or coaxial and electrical connectors to fluids or solvents. If these components get wet, the system may not function properly. This may lead to patient injury.

Fluoroscopy required for catheter placement – The use of fluoroscopy during catheter ablation procedures presents the potential for significant x-ray exposure to both patients and laboratory staff. Extensive exposure may result in acute radiation injury and increased risk for somatic and genetic effects. Only perform catheter ablation after giving adequate attention to the potential radiation exposure associated with the procedure, and taking steps to minimize this exposure. Give careful consideration before using the device in pregnant women.

For single use only – This device is intended only to be used once for a single patient. Do not reprocess or resterilize this device for the purpose of reuse. Reuse, reprocessing, or resterilization may compromise the structural integrity of the device or create a risk of contamination of the device that could result in patient injury, illness, or death.

Frequent flushing of the guide wire lumen – Flush the guide wire lumen before initial insertion and then frequently throughout the procedure to prevent coagulation of blood in the lumen. Flush the guide wire lumen with heparinized saline after each contrast injection.

Guide wire compatibility – Use only 0.081 cm (0.032 in) or 0.089 cm (0.035 in) guide wires with the catheter. Using another guide wire may damage the catheter or compromise the procedure.

Improper connection – Do not connect the cryoablation catheter to a radiofrequency (RF) generator or use it to deliver RF energy. This may cause catheter malfunction or patient injury.

Induced arrhythmias – Catheter procedures may mechanically induce arrhythmias.

Leakage current from connected devices – Use only isolated equipment (IEC 60601-1 Type CF equipment, or equivalent) with the CryoConsole and catheters or patient injury or death may occur.

Other catheters, devices, or wires – Avoid catheter entanglement with other catheters, devices, or wires. Such entanglement may necessitate surgical intervention.

Phrenic nerve impairment – To reduce the potential for phrenic nerve impairment, perform the following steps:

- Position the balloon as antral as possible and not in the tubular portion of the pulmonary vein. To ensure proper catheter position, observe the balloon shape and the balloon position within the anatomy.
- Monitor the status of the phrenic nerve continuously during right-sided pulmonary vein applications using an appropriate monitoring technique. One common monitoring technique is to continuously pace the phrenic nerve throughout each cryoablation application of the right pulmonary veins. While pacing, monitor diaphragm contraction by placing a hand on the abdomen to assess for loss of capture or changes in the strength of the diaphragmatic contraction.
- Stop ablation immediately if phrenic nerve impairment is observed.

Post-ablation period – Closely monitor patients undergoing cardiac ablation procedures during the post-ablation period for clinical adverse events.

Pressurized refrigerant – The catheter contains pressurized refrigerant during operation. Release of this gas into the circulatory system due to equipment failure or misuse may result in gas embolism.

Pulmonary vein narrowing or stenosis – Catheter ablation procedures inside or near pulmonary veins may induce pulmonary vein narrowing or stenosis. Do not ablate in the tubular portion of the pulmonary vein. The occurrence of this complication may necessitate percutaneous angioplasty or surgical intervention. Seven of 228 (3.1%) cryoablated study subjects had one or more stenosed pulmonary veins (PVs) detected during study imaging. (See *Section 5.8* for study results.)

Qualified users – This cryoablation system should be used only by or under the supervision of physicians trained in cryoablation procedures.

Required use environment – Cryoablation procedures should be performed only in a fully equipped facility.

RF ablation – Before powering up an RF generator or applying RF energy, disconnect the cryoablation catheter from the CryoConsole to avoid an error message and unnecessary catheter replacement.

Septal damage – Always deflate the balloon and withdraw the balloon into the transseptal sheath before removing the balloon from the left atrium. Crossing the septum while the balloon is unsheathed, inflated, or inflating in the septal puncture site may cause serious septal damage.

Steerable sheath compatibility – Use only a compatible Medtronic 12 Fr inner diameter sheath with the Arctic Front Advance Pro Cryoballoon. Using another sheath may damage the catheter or balloon segment.

Sterile package inspection – Inspect the sterile packaging and catheter before use. If the sterile packaging or catheter is damaged, do not use the catheter. Contact your Medtronic representative.

System compatibility – Use only Medtronic cryoablation catheters, refrigerant tanks, and components with the CryoConsole. The safety and use of other catheters or components has not been tested.

5 Clinical summary

Study title:	STOP-AF: A Randomized, Controlled Clinical Trial of Catheter Cryoablation in the Treatment of Paroxysmal Atrial Fibrillation
Number of centers:	26 centers in the United States and Canada
Number of subjects:	245 randomized subjects

5.1 Study purpose

To evaluate the safety and effectiveness of the Arctic Front Cardiac Cryoablation Catheter System, including the FlexCath Steerable Sheath, Freezor MAX Cardiac Cryoablation Catheter, and CryoConsole (Gen V) in adult patients with paroxysmal atrial fibrillation who have failed one or more Atrial Fibrillation drugs.

5.2 Study scope, design and methods

The study was a prospective, randomized, controlled, multicenter, pivotal clinical investigation conducted at 26 investigational sites (23 in the United States and 3 in Canada). Subjects with paroxysmal atrial fibrillation (PAF) referred for ablative intervention after efficacy failure of one or more Study Atrial Fibrillation (AF) Drugs (flecainide, propafenone, or sotalol) (Amiodarone was not considered a study AF Drug) were randomized 2:1 to cryoablation intervention (Experimental Subjects, ES) or to a Study AF Drug (Control Subjects, CS). Subjects were followed for 12 months with scheduled and symptom-driven assessments to detect recurrent atrial fibrillation by means of periodic electrocardiograms, weekly scheduled trans-telephonic monitoring, patient-initiated trans-telephonic monitoring, and 24-hour Holter monitoring at 6 and 12 months. The first 90 days after study therapy was initiated was considered a blanked period for all subjects.

5.3 Study endpoints

The primary effectiveness outcome was Treatment Success, defined on the basis of Chronic Treatment Failure events and the occurrence of Acute Procedural Success.

- **Treatment Success:** (TS), defined for CS as freedom from any Chronic Treatment Failure events, and for ES as both Acute Procedural Success **and** freedom from Chronic Treatment Failure from Day 0 through the 12 month follow-up visit. This comparison of proportions was to be performed using a 2-sided Fisher's Exact Test of binomial proportions with a = 0.05 and b = 0.20, with an estimate of TS in the groups of 40% Control and 60% Experimental and a 2:1 randomization, giving a sample size calculation of 240 evaluable subjects.
  - **Acute Procedural Success:** (APS), defined as the electrical isolation of ≥ 3 pulmonary veins from the left atrium (as reported after the first procedure) was an additional primary effectiveness outcome measure, for ES only.
  - **Chronic Treatment Failure:** (CTF), defined as Detectable AF (during the Non Blanked Follow-up Period), the use of Non Study AF Drugs, or an AF Intervention (Day 0 through the 12 month follow-up).

The initial cryoablation treatment date or the first day of AF Drug therapy was considered the Start Date for all subjects. Subjects were then followed for 12 months from their Start Date with scheduled and symptom-driven assessments to detect recurrent AF (Detectable AF) by means of periodic electrocardiograms (ECG), weekly scheduled transtelephonic monitoring (TTM), subject-initiated TTMs, and 24-hour Holter monitoring at 6- and 12- months. The 90 day interval following the Start Date was considered a Blanked Follow-up Period for all subjects. It was during this time period that the Control Subjects underwent AF Drug optimization and that Experimental Subjects were allowed one repeat cryoablation as needed. Occurrences of AF during the Blanked Follow-up Period were not considered as Chronic Treatment Failure (CTF) and did not count as an event against the primary objective. Control Subjects were allowed one crossover cryoablation treatment only after they demonstrated CTF. All repeat and crossover cryoablations required review and approval by the Medical Monitor or Principal Investigator.

The primary safety outcomes were Cryoablation Procedure Events and Major Atrial Fibrillation Events.

- **Cryoablation Procedure Events:** (CPE) defined for ES **only** as specifically categorized device- or procedure-related serious adverse events (SAE) with onset within 7 days of cryoablation (access site complications, cardiac damage, embolic complications, arrhythmias, persistent phrenic nerve palsy, or death) or with onset at any time through 12 months of follow-up (pulmonary vein stenosis or atrio-esophageal fistula). (*Table 1*)

Table 1. Cryoablation Procedure Event Categories

Cryoablation Procedure Events (CPE)	With onset between Day 0 and:
Access site complications requiring • Transfusion of 3 or more units; or • Surgical intervention; or • Permanent loss of functional impairment	Day 7
Cardiac damage (including MI)	Day 7
• Pulmonary vein stenosis	12-month follow-up visit[a]
• Atrio-esophageal fistula	12-month follow-up visit[a]
Embolic complications (including stroke)	Day 7
Arrhythmias	Day 7
Persistent phrenic nerve palsy	Day 7
Death	Day 7

[a] This CPE will be assessed through the completion of within window study follow-up.

- **Major Atrial Fibrillation Events:** (MAFE) defined for CS and ES as serious adverse events in the categories of cardiovascular death, myocardial infarction, stroke, or any hospitalization primarily related to AF recurrence/ablation, atrial flutter ablation (excluding Type I), systemic embolization, congestive heart failure, hemorrhagic event or anti-arrhythmic drug initiation, adjustment or complication. (*Table 2*)

Table 2. Major Atrial Fibrillation Events Categories

Major Atrial Fibrillation Events (MAFE)
Cardiovascular death
Myocardial infarction (MI)
Stroke
Associated with or leading to a hospitalization for (primary reason): • AF recurrence or ablation • Atrial flutter ablation (excluding Type I) • Systemic embolization (not stroke) • Congestive heart failure • Hemorrhagic event (not stroke) • Anti-arrhythmic drug initiation, adjustment, or complication

5.4 Subject accountability

Enrollment and accountability are summarized in the following table.

Table 3. Subjects accountability and disposition

Subject disposition	Control subjects	Experimental subjects	All subjects
Subjects provisionally enrolled and randomized	87	171	258
Screen failures	1	5	6
Withdrawal of consent	4	3	7
Subjects enrolled	82	163	245
Death	0	1	1
Lost to follow-up	0	0	0
Withdrawal of consent	3	0	3
Subjects completing 12 month follow-up	79	162	241
Control subjects crossing over to cryoablation	65	----	----
Experimental subjects undergoing reablation	----	31	----

Study populations for analysis were:

- Safety Population (n = 245): pre-specified, included **all** subjects (82 CS, 163 ES) who were enrolled, randomized, and received treatment.
- Effectiveness Populations
  - Modified intent-to-treat (n = 245): pre-specified included **all** subjects (82 CS, 163 ES) who were enrolled, randomized, and received treatment.
  - Per protocol Population (n = 181): pre-specified, included those subjects that received treatment in their randomized group and completed the Blanked Follow-up Period, having complete assessments for detection of AF through 12 months of follow-up including at least 80% compliance with rhythm monitoring, and having the absence of any major protocol violations.
- Cryoablated Control Population (n = 65): pre-specified, included those CS who underwent crossover cryoablation. Control subjects were allowed to undergo one cryoablation procedure under the protocol. All control subject crossovers were required to be approved by the Principal Investigator or Medical Monitor. Cryoablated control subjects were followed for 12 months from the date of the cryoablation procedure.
- Reablated Experimental Population (n = 31): pre-specified, included ES who underwent repeat cryoablation during the Blanked Follow-up Period. Experimental subjects were allowed to undergo an additional cryoablation procedure during the 90 day blanking period. Reablated experimental subjects maintained the same follow-up schedule as determined by initial study cryoablation procedure.

5.5 Subject demographics

The STOP AF study population consisted of mostly white ethnic background (94.3%), had a mean age of 56.6 years with 77.1% being male. The baseline characteristics were comparable between the randomized groups, as summarized in *Table 4* and *Table 5*.

Table 4. Baseline demographics - age, echocardiography, AF symptoms, SF-36 score

	All subjects mean (SE) N median (min, max) N = 245	Control subjects mean (SE) N median (min, max) N = 82	Experimental subjects mean (SE) N median (min, max) N = 163	Difference [95% 95%C][a]	p value
Age (years)	56.6 (0.60) 245 57.0 (26, 75)	56.4 (1.04) 82 56.5 (26, 72)	56.7 (0.73) 163 58.0 (33, 75)	0.3 [–2.2, 2.8]	0.797
Left atrial AP diameter (mm)	40.5 (5.4) 245 40 (24, 54)	40.9 (6.0) 82 40.5 (28, 54)	40.3 (5.1) 163 40 (24, 50)	–0.7 [–2.1, -0.8]	0.353
Left ventricular EF (%)	60.2 (5.6) 244 60 (40, 76)	60.7 (6.4) 82 60 (45, 76)	60.0 (5.7) 162 60 (40, 75)	–0.7 [–2.3, -0.9]	0.407
Symptomatic AF in the 2 months prior to enrollment	23.2 (2.54) 239 10.0 (2, 300)	21.2 (3.63) 80 10.0 (2, 250)	24.3 (3.36) 159 10.0 (2, 300)	3.0 [–7.6, 13.7]	0.540
Overall SF-36 score	70.63 (1.115) 231 74.0 (15.0, 98.0)	70.37 (1.716) 78 74.50 (29.0, 98.0)	70.76 (1.442) 153 74.00 (15.0, 98.0)	0.4% [–4.3, 5.0%]	0.870

[a] AP = Antero-posterior; EF = Ejection Fraction

Table 5. Baseline demographics - gender, ethnicity and NYHA Class

		All subjects % (n) N = 245	Control subjects % (n) N = 82	Experimental subjects % (n) N = 163	p value
Gender	Male	77.1% (189)	78.0% (64)	76.7% (125)	0.873
	Female	22.9% (56)	22.0% (18)	23.3% (38)	
Ethnicity	White	94.3% (231)	92.7% (76)	95.1% (155)	0.696
	Black	1.2% (3)	2.4% (2)	0.6% (1)	
	Hispanic	0.8% (2)	1.2% (1)	0.6% (1)	
	Asian	1.6% (4)	1.2% (1)	1.8% (3)	
	Other	2.0% (5)	2.4% (2)	1.8% (3)	
NYHA[a] Class	None / Class I	93.5% (229)	93.9% (77)	93.3% (152)	1.000
	Class II	6.5% (16)	6.1% (5)	6.7% (11)	
Cardiovascular risk factors	Diabetes	7.3% (18)	8.5% (7)	6.7% (11)	0.612
	Hypertension	42.4% (104)	45.1% (37)	41.1% (67)	0.585
	Dyslipidemia	48.2% (118)	48.8% (40)	47.9% (78)	0.893

[a] NYHA = New York Heart Association

Previously failed AF Drugs for efficacy were comparable between study groups with 36% of all study subjects having failed flecainide, 47% having failed propafenone, and 29% having failed sotalol.

5.6 Results

Procedural data

The Arctic Front Cryocatheter parameters for first procedures in ES (n = 163) included approximately 3 cryoapplications for each of the 4 major pulmonary veins at a mean intra-catheter temperature between -48.6 and -54.1°C, with a median duration of 240 s per cryoapplication (*Table 6*).

Table 6. Arctic Front Cryocatheter Cryoapplication Parameters by Pulmonary Vein Location, First Experimental Procedures (N = 163)

Cryoapplication parameters	RSPV[a] mean (SE) N median (min, max)	RIPV[a] mean (SE) N median (min, max)	LSPV[a] mean (SE) N median (min, max)	LIPV[a] mean (SE) N median (min, max)
# of cryo apps	2.9 (0.12) 161	2.8 (0.14) 154	3.6 (0.14) 150	3.2 (0.11) 152

Table 6. Arctic Front Cryocatheter Cryoapplication Parameters by Pulmonary Vein Location, First Experimental Procedures (N = 163) (continued)

Cryoapplication parameters	RSPV[a] mean (SE) N median (min, max)	RIPV[a] mean (SE) N median (min, max)	LSPV[a] mean (SE) N median (min, max)	LIPV[a] mean (SE) N median (min, max)
	3.0 (1, 11)	2.0 (0, 11)	3.0 (1, 12)	3.0 (1, 9)
Measured temp (°C)	–50.70 (0.73) 460 –51.0 (–80.0, 33.0)	–48.63 (1.00) 405 –48.0 (–81.0, 35.0)	–54.12 (0.79) 508 –55.0 (–81.0, 36.0)	–50.78 (0.78) 484 –49.0 (–81.0, 33.0)
Duration (secs)	196.9 (3.54) 473 240.0 (3, 240)	205.4 (3.69) 428 240.0 (3, 240)	219.3 (2.80) 534 240.0 (1, 240)	230.1 (2.07) 488 240.0 (4, 360)

[a] PV = pulmonary vein, R = right, L = left, I = inferior, S = superior.

The Freezor MAX Cryocatheter was used for gap cryoablations in a small proportion of major pulmonary veins during first experimental procedures (initial study cryoablation procedure). (*Table 7*)

Table 7. Freezor MAX Cryocatheter Use by Pulmonary Vein Location, First experimental procedures (N = 163)

Freezor MAX Cryocatheter Use	RSPV[a]% (n)	RIPV[a]% (n)	LSPV[a]% (n)	LIPV[a]% (n)
Experimental first procedures	4.9% (8)	9.2% (15)	4.3% (7)	4.3% (7)

[a] PV = pulmonary vein, R = right, L = left, I = inferior, S = superior.

The first experimental procedure lasted a mean of 371 min, with investigational devices inserted in the subject vasculature for a mean of 181 min. Cryoablation time averaged 65.7 min, and total fluoroscopy time averaged 62.8 min (*Table 8*).

Table 8. Cryoablation procedural durations, First experimental procedures (N = 163)

Procedure, Cryocatheter & fluoroscopy times	Total procedure duration mean (SE) N median (min, max)	Cryocatheter insertion time mean (SE) N median (min, max)	Total ablation time mean (SE) N median (min, max)	Total fluoroscopy time mean (SE) N median (min, max)
Experimental first procedures (min)	371.4 (7.89) 163 349.0 (200.0, 650.0)	181.2 (5.86) 162 169.0 (72.0, 427.0)	65.7 (2.70) 162 56.8 (17.0, 179.8)	62.8 (2.55) 162 54.0 (8.0, 229.0)

Compliance with follow-up and rhythm monitoring requirements

Follow-up compliance with key assessments was high, exceeding 90% in all cases except for Holter compliance which was as low as 72% at the 6 month follow-up visit in the Control group. The Holter monitoring assessment protocol requirements for cryoablated control subjects was reduced because cryoablated control subjects were considered chronic treatment failures. This meant further Holter monitoring was not required.

Pulmonary vein CT/MRI imaging was performed prior to a subjects first cryoablation procedure (Experimental and Cryoablated Control) as well as at 6 and 12 months post-cryoablation procedure for pulmonary vein stenosis surveillance (*Table 9*).

Effectiveness outcomes and measures

Table 9. Compliance with follow-up and monitoring requirements

Parameter		Control subjects %[a]	Experimental subjects %[b]	All subjects %[c]
Office visits	3 months	98.8%	100.0%	99.6%
	6 months	97.6%	100.0%	99.2%
	12 months	96.3%	99.4%	98.4%
Weekly TTMs		91.5%	91.5%	91.5%
Scheduled TTMs[d]		3,841	7,983	11,824
Unscheduled TTMs[d]		3,016	2,084	5,100
24° h Holter monitors	6 months[e]	72.8%	85.9%	81.6%
	12 months[f]	74.7%	88.9%	84.2%
Imaging of pulmonary veins	Baseline	100%	100%	100%
	6 months	95.4%	96.9%	96.5%
	12 months	93.8%	97.5%	96.4%

[a] Denominator = 82 except for imaging of pulmonary veins for which denominator = 65 cryoablated Control Subjects eligible for 6 month study and 47 eligible for 12 month study at time of report.

[b] Denominator = 163 Experimental Subjects.

[c] Denominator = 245 except for imaging of pulmonary veins for which denominator = 228 cryoablated subjects eligible for 6 month study and 205 eligible for 12 month study at time of report.

[d] Number of TTM recordings

[e] Has a holter recording between 150 and 210 days

[f] Has a holter recording between 335 and 395 days

The STOP AF trial defined three (3) Primary Effectiveness Outcome Measures:

- **Acute Procedural Success (APS)**, the electrical isolation of ≥ 3 pulmonary veins from the left atrium as reported after the first procedure (ES).
- **Chronic Treatment Failure (CTF)**, defined as Detectable AF during the Non Blanked Follow-up Period, or use of Non Study AF Drugs, or an AF Intervention through the 12 month follow-up visit. The protocol stipulated that subjects could not be counted as a CTF for Detectable AF during the 90 day blanking period. However, subjects could have a CTF for use of Non Study AF Drugs or AF Intervention during the 90 day blanking period.
- **Treatment Success (TS)**, defined as:
  - **Experimental Subjects:** Acute Procedural Success and Freedom from Chronic Treatment Failure.
  - **Control Subjects:** Freedom from Chronic Treatment Failure.

Acute Procedural Success: Acute Procedural Success was achieved in 98.2% of ES. Electrical isolation was achieved in >95% of each of the 4 main pulmonary veins attempted. Electrical isolation was assessed by pacing to determine electrical conduction between the pulmonary vein and left atrium had been interrupted, by evidence of entrance and, where assessable, exit block (*Table 10*).

Table 10. Experimental First Procedures: Acute Pulmonary Vein Isolation rates

Vein(s)	Proportion isolated % (n / N)
≥ 3 PVs (APS[a])	98.2% (160 / 163)
RSPV[b]	98.1% (159 / 163)
RIPV[b]	97.4% (152 / 156)
LSPV[b]	96.7% (146 / 151)
LIPV[b]	97.4% (149 / 153)

[a] APS = Acute Procedural Success

[b] PV = pulmonary vein, R = right, L = left, I = inferior, S = superior

Treatment Success: The Primary Effectiveness Outcome, Treatment Success, was observed in 69.9% of ES and 7.3% of CS (difference 62.6%, p < 0.001). (See *Figure 2* and *Table 11*).

Figure 2. Kaplan Meier Display of Continued Treatment Success by Group Through 12 months, Modified Intent to Treat Population

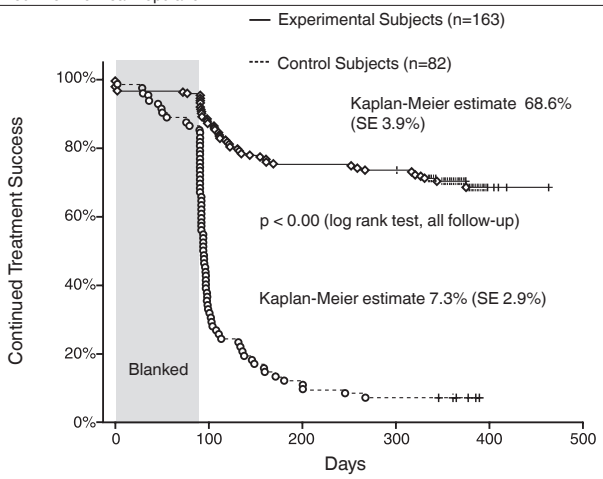


Table 11. Primary effectiveness outcome: Treatment success (mITT Population)

Primary effectiveness outcome	Control subjects % (n / N) [95% CI]	Experimental subjects % (n / N) [95% CI]	Difference [95% CI]	p value
Treatment success	7.3% (6 / 82) [2.7, 15.2%]	69.9% (114 / 163) [62.3, 76.9%]	62.6% [53.6, 71.6%]	<0.001

Additional Measures of Effectiveness: Other relevant measures confirmed treatment effectiveness for PAF:

- **AF Drug Free Treatment Success:** Of the 114 ES with Treatment Success, 101 (62.0%) were Treatment Successes without the use of any AF Drugs at any time during the Non Blanked Follow-up Period.
  - 62.0% (101/163) of experimental subjects were off AF drugs during the entire non-blanked follow-up period, while 8% (13/163) of the experimental subjects that were considered treatment successes were treated with a previously failed AF drug during the non-blanked follow-up period (*Table 11*).

Table 12. Treatment Success and Atrial Fibrillation Drug Therapy

AF Drug Status during Non-Blanked Follow-up Period	Control Subjects % (n / N) [95% CI] N = 82	Experimental Subjects % (n / N) [95% CI] N = 163
Treatment Success	7.3% (6 / 82) [2.7, 15.3%]	69.9% (114 / 163) [62.3, 76.9%]
Treatment Success Without Any AF Drugs	0.0% (0 / 82) [0.0, 4.4%]	62.0% (101 / 163) [54.0, 69.4%]
Treatment Success With Any AF Drugs	7.3% (6 / 82) [2.7, 15.3%]	8.0% (13 / 163) [4.3, 13.3%]

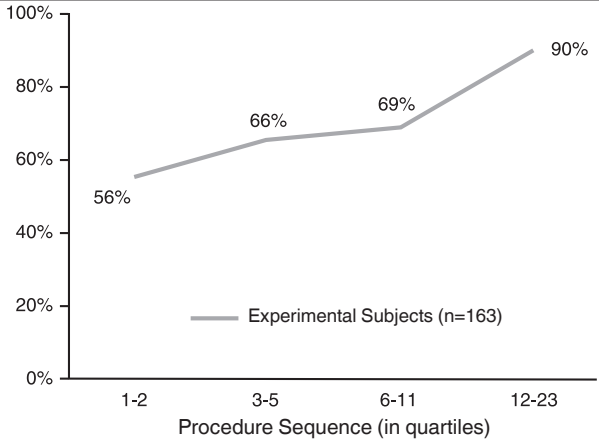
- **Reduced Use of AF Drugs:** 74% of all ES were off AF Drugs during the last 3 months of follow-up, and 87% of ES with Treatment Success were free from any AF Drug use during the last 3 months of follow-up.
- **Improved Quality of Life:** ES showed significantly improved SF-36 quality of life score through 12 months of follow-up in every subscale.
- **Reduced Symptoms:** ES had a significant reduction in AF symptomatic burden after cryoablation. At baseline 100% of patients had symptoms, at 12 months only 20% had symptoms from PAF.
- **Effectiveness by Balloon Size**: Treatment success was 70% among cryoablations with balloon size 23 mm, 63.3% among cryoablations with balloon size 28 mm, and 76.2% among subjects with both balloon sizes utilized (*Table 12*).

Table 13. Primary Effectiveness Outcome; Proportion of ES with Treatment Success at the 12 Month Follow-up Visit

Cohort	Experimental Subjects % (n / N) [95% CI] N = 163
Treatment success	69.9% (114 / 163) [62.3, 76.9%]
By balloon size:	
Balloon size 23 only	70% (35 / 50) [55.4, 82.1%]
Balloon size 28 only	63.3% (31 / 49) [48.3, 76.6%]
Both balloon sizes	76.2% (48 / 63) [63.8, 86.0%]

- **Effectiveness by number of procedures performed**: A post-hoc analysis revealed that procedure sequence had an impact on treatment success in the STOP AF trial. *Figure 3* illustrates that treatment success improved as the number of procedures performed increased at a given site (see *Table 12* and *Figure 3*).

Figure 3. Procedure Frequency and Treatment Success



Atrial Flutter: Adjunctive cryoablation of the cavo-tricuspid isthmus (CTI) was performed in 66 ES.Bidirectional block was achieved in 97.0% of these subjects at the first attempt. Freedom from Flutter Chronic Treatment Failure (Flutter CTF) was observed in 70.7% (29 / 41) of those subjects with a history of atrial flutter at baseline and 84.0% (21 / 25) of those subjects with no history of atrial flutter at baseline.

5.7 Safety outcomes and measures

Serious Adverse Events were defined as any undesirable clinical occurrence in a study subject that included any of the following events:

- Any adverse event resulting in death
- Any adverse event, which is life-threatening
- Any adverse event resulting in inpatient hospitalization > 48 hours or prolongation of existing hospitalization by two or more days
- Any adverse event resulting in a persistent, significant disability or incapacity
- Any adverse event resulting in a congenital anomaly or birth defect

Primary Safety Outcome Measures were defined as:

- **Cryoablation Procedure Events** (CPEs), assessed only for ES for procedural safety, which were device or procedure-related serious adverse events (SAE) categorized as access site complications, cardiac damage, PV stenosis, embolic complications, arrhythmias, unresolved phrenic nerve palsy, and death; and
- **Major Atrial Fibrillation Events** (MAFEs), which were serious adverse events categorized as cardiovascular death, myocardial infarction, stroke, or hospitalization for AF. Overall disease and treatment morbidity, exclusive of the experimental cryoablation procedure, was assessed for both the control and experimental treatment subjects by this measure.

Primary Safety Outcomes (two were defined by the STOP AF Study Protocol):

- The proportion of experimental group safety subjects with one or more CPEs.
- The proportion of safety subjects in either group free of MAFEs at the 12 month follow-up visit.

Both safety outcomes met pre-specified criteria and success was achieved for the safety evaluation.

Cryoablation Procedure Events: Data for subjects who were randomized to the experimental therapy and received treatment are included in the analysis of CPE shown in the following table. ES had a 3.1% (6.3% UCB) rate of CPE compared to a pre-specified UCB of 14.8% ($p < 0.001$). Observed CPEs included 2 instances of cardiac damage (one peri-procedural MI, one perforation with tamponade), one arrhythmia, and two cases of pulmonary vein stenosis (*Table 14*).

Table 14. Primary safety outcome: Cryoablation procedure events

Primary safety outcome: CPE	Experimental subjects % (n / N)	95% upper confidence bound	p value
Experimental subjects with one or more CPE	3.1% (5 / 163)	6.3%	<0.001

Table 15 lists the individual CPEs that were reported during the STOP AF trial.

Table 15. Experimental Subjects; Cryoablation Procedure Event Categories

CPE Categories	Experimental Subjects% (n) N = 163	95% One-Sided Upper Confidence Bound[a]
Access site complications	0.0% (0)	1.8%
Cardiac damage (including myocardial infarction)	1.2% (2)	3.8%
Embolic phenomena (including stroke)	0.0% (0)	1.8%
Arrhythmias	0.6% (1)	2.9%
Persistent phrenic nerve injury[b]	0.0% (0)	1.8%
Death	0.0% (0)	1.8%
Pulmonary vein stenosis[c]	1.2% (2)	3.8%

[a] Based on Clopper-Pearson confidence intervals

[b] Four (4) Experimental subjects had phrenic nerve injury persisting at 12-months of follow-up; none were adjudicated as SAE. They were not included as a CPE because they were not adjudicated as an SAE.

[c] Five (5) Experimental Subjects had one or more pulmonary veins with stenosis during study follow-up; 2 of these adverse events were adjudicated as SAE.

Pulmonary Vein Stenosis: The PV stenosis rate was 3.1% (5/163) in ES and 3.1% (7/228) for all subjects having undergone cryoablation (*Table 16*). Stenosis was defined in the protocol as a reduction in the calculated pulmonary vein cross sectional area to <25% of the baseline pulmonary vein cross sectional area. Five (5) subjects had radiologic findings only, without symptoms of any kind. Two (2) subjects experienced significant symptoms and disability (i.e. Serious Adverse Event) and therefore these two pulmonary vein stenosis events were adjudicated as a CPE.

Table 16. Occurrence of Pulmonary Vein Stenosis in Cryoablated Subjects

Proportion of Subjects	Experimental			Control	All Subjects
	One Cryoablation[a] % (n) [95% CI][b]	Two Cryoablations (n) [95% CI][b]	Any Cryoablation % (n) [95% CI][b]	One Cryoablation (n) [95% CI][b]	Any Cryoablation (n) [95% CI][b]

Table 16. Occurrence of Pulmonary Vein Stenosis in Cryoablated Subjects (continued)

Proportion of Subjects	Experimental			Control	All Subjects
	N = 132	N = 31	N = 163	N = 65	N = 228
Stenosis in ≥1 PV at 6 or 12 Months[c]	2.3% (3) [0.5, 6.5%]	6.5% (2) [0.8, 21.4%]	3.1% (5) [1.0, 7.0%]	3.1% (2) [0.4, 10.7%]	3.1% (7) [1.2, 6.2%]

[a] One ES also had RF ablation for atrial fibrillation 72 days after the initial cryoablation.

[b] Clopper-Person confidence intervals.

[c] Each subject is counted only once within each time point.

CI = confidence interval, PV = pulmonary vein.

Phrenic Nerve Palsy: Twenty-nine (29) occurrences of Phrenic Nerve Palsy (PNP) in 28 subjects were reported (*Table 17*). Overall, 11.2% (29 / 259) of all cryoablation procedures were associated with PNP. Twenty-five (25) (11%) were associated with PNP, which resolved within 12 months of follow-up, and 4 (1.8%) were associated with persistent PNP (*Table 18*). Fifteen (15) subjects were asymptomatic, 13 had one or more associated symptoms including dyspnea on exertion (6), dyspnea (5), shortness of breath (2), orthopnea (2) and cough (1) during the period in which hemi-diaphragmatic abnormalities were noted. One occurrence of PNP was adjudicated as an SAE.

Table 17. Phrenic Nerve Palsy; Procedures

Phrenic Nerve Palsy	First Experimental Ablation Subjects % (n) [95% CI] N = 163[a]	Experimental Reablation Subjects % (n) [95% CI] N = 31[a]	Crossover Control Ablation Subjects % (n) [95% CI] N = 65[a]	All Ablated Subjects % (n) [95% CI] N = 228[a]
Procedures free of PNP[b]	87.7% (143) [81.7, 92.3%]	90.3% (28) [74.2, 98.0%]	90.8% (59) [81.0, 96.5%]	88.8% (230) [84.3, 92.4%]
Procedures associated with PNP[b]	12.3% (20) [7.7, 18.3%]	9.7% (3) [2.0, 25.8%]	9.2% (6) [3.5, 19.0%]	11.2% (29) [7.6, 15.7%]

[a] N = the total number of subjects undergoing cryoablation procedures of this type.

[b] One subject had 2 events of PNP, one with the first experimental cryoablation and one with the second, reablation procedure (both of which resolved).

Table 18. Phrenic Nerve Palsy; Subjects

Phrenic Nerve Palsy	First Experimental Ablation Procedures % (n) [95% CI] N = 163[a]	Experimental Reablation Procedures % (n) [95% CI] N = 31[a]	Crossover Control Ablation Procedures % (n) [95% CI] N = 65[a]	All Ablation Procedures % (n) [95% CI] N = 259[a]
All Subjects with PNP	12.3% (20) [7.6, 18.3%]	9.7% (3) [2.0, 25.8%]	9.2% (6) [3.5, 19.0%]	12.3% (28) [8.3, 17.3%]
Persistent PNP (radiographic)	2.5% (4) [0.7, 6.2%]	0.0% (0) [0.0, 11.2%]	0.0% (0) [0.0, 5.5%]	1.8% (4) [0.5, 4.4%]
Resolved PNP (radiographic)	9.8% (16) [5.7, 15.5%]	9.7% (3) [2.0, 25.8%]	9.2% (6) [3.5, 19.0%]	11.0% (25) [7.2, 15.8%]

[a] N = the total number of cryoablation procedures of this type.

Major Atrial Fibrillation Events: Data for subjects who were randomized to either experimental or drug treatment, received such treatment and were followed through 12 months post treatment start are included in the analysis for MAFE shown in the following table. The analysis was an evaluation of non-inferiority of MAFE rates in ES compared to Control. The clinically significant difference (δ) for establishing noninferiority for the MAFE free rate was set at 10% ES had a 96.9% Freedom from MAFE rate, compared to CS who had a 91.5% rate ($p < 0.0001$, non-inferiority for difference ≤ 10%) (see *Table 19*).

Table 19. Primary safety outcome: Freedom from MAFE

Primary safety outcome: Freedom from MAFE	Control subjects % (n /N) [95% CI]	Experimental subjects % (n / N) [95% CI]	Difference [95% CI]	Test for non-inferiority d = 0.10 p value
Freedom from MAFE (through 12 month follow-up)	91.5% (75 / 82) [83.2, 96.5%]	96.9% (158 / 163) [93.0, 99.0%]	5.4% [–1.1, 12.1%]	<0.001

The observed categories of MAFEs are displayed for both treatment groups below (*Table 20*).

Table 20. Subjects with one or more MAFEs by category, safety population

MAFE Categories	Control subjects% (n / N) [95% CI]	Experimental subjects % (n / N) [95% 95% CI]	Difference [95% CI]	p value
Any MAFE	8.5% (7 / 82) [3.5, 16.8%]	3.1% (5 / 163) [1.0, 7.0%]	–5.4% [–12.1, 1.1%]	0.112
Cardiovascular death	0.0% (0 / 82) [0.0, 4.4%]	0.6% (1 / 163) [0.0, 3.4%]	0.6% [–0.6, 1.8%]	1.000
Hospitalization for:	7.3% (6 / 82) [2.7, 15.2%]	1.8% (3 / 163) [0.4, 5.3%]	–6.5% [11.5, 0.5%]	0.064
AF recurrence or ablation	6.1% (5 / 82) [2.0, 13.7%]	0.6% (1 / 163) [0.0, 3.4%]	–5.5% [–10.8, –0.2%]	0.017
Atrial flutter ablation (excluding Type I)	1.2% (1 / 82) [0.0, 6.6%]	0.0% (0 / 163) [0.0, 2.2%]	–1.2% [–3.6, 1.2%]	0.335
Systemic embolization (not stroke)	0.0% (0 / 82) [0.0, 4.4%]	0.0% (0 / 163) [0.0, 2.2%]	NA	NA
Congestive heart failure	0.0% (0 / 82) [0.0, 4.4%]	1.2% (2 / 163) [0.1, 3.4%]	–1.2% [–5.0, 2.5%]	1.000
Hemorrhagic event (not stroke)	2.4% (2 / 82) [0.3, 8.5%]	1.2% (2 / 163) [0.1, 4.4%]	–1.2% [–5.0, 2.5%]	0.603
Anti-arrhythmic drug: initiation, adjustment, or complication[a]	4.9% (4 / 82) [1.3, 12.0%]	0.6% (1 / 163) [0.0, 3.4%]	–4.3% [–9.1, 0.5%]	0.044
Myocardial infarction	0.0% (0 / 82) [0.0, 4.4%]	0.6% (1 / 163) [0.0, 3.4%]	0.6% [–0.6, 1.8%]	1.000
Stroke	0.0% (0 / 82) [0.0, 4.4%]	0.6% (1 / 163) [0.0, 3.4%]	0.6% [–0.6, 1.8%]	1.000

[a] Excludes control subject treatment initiation

As described in *Table 21*, only 1 ES had a MAFE categorized as stroke. There was an additional 4 (3 ES and 1 CS) strokes reported during the 12 month follow-up. All 4 subjects had recovered completely at the time of the 12 month follow-up. *Table 21* provides additional detail for the 5 strokes that were reported during the 12 month follow-up (1 MAFE stroke, 4 non-MAFE stroke).

Table 21. Subjects with Stroke During Study Follow-up

Group	Diagnosis (verbatim)	Onset	Ablation Related[a]	Clinical Outcome	Event Severity	SAE
Exp	Small hemorrhagic stroke	Day 183	No	Recovered completely	Mild	No
Exp	Lacunar infarct	Day 51	Unknown[b]	Recovered completely	Mild	No
Cont	Stroke	Same day as X-over ablation	Yes	Recovered completely	Severe	No
Exp	"Sees white spots in both eyes"	~1 month after cryoablation	No	Recovered completely	Mild	No
Exp	Subarachnoid hemorrhage	Day 260	No	Recovered completely	Severe	Yes

[a] Ablation-related = procedure-related or device-related adverse event.

[b] Age of infarct indeterminate when discovered and could not be temporally linked to procedure or device. Adjudicated as of unknown relatedness

Exp = Experimental, Cont = Control, X-over = crossover

5.8 Additional safety information from the STOP AF Pivotal Trial

Serious adverse events (SAE)

A total of 55 serious adverse events (SAE) in 32 study subjects were reported by Investigators during the first 12 months of study follow-up (See *Table 22*). Twenty-two (22) SAE occurred in 12 CS (12 MAFE and 10 other SAE) (See *Table 23*) and 33 SAE occurred in 20 ES (5 CPE, 8 MAFE and 20 other SAE) (See *Table 22*). The overall proportion of CS with one or more SAE was 14.6% and for ES was 12.3%, a slightly lower rate of SAE occurrence that was not significantly different (p = 0.688).

Table 22. Subjects with one or more serious adverse events, safety population

Serious adverse events	Control subjects % (n /N)	Experimental subjects % (n / N)	Difference [95% CI]	p value
Serious adverse events	14.6% (12 / 82)	12.3% (20 / 163)	-2.3% [–11.5, 6.8%]	0.688

The SAE occurring in CS and ES are listed in the following tables (*Table 23* and *Table 22*).

Table 23. Serious adverse events occurring in control subjects, safety population

Serious Adverse Events	Control Subjects % (n / n) N=82
Atrial Fibrillation	4.9% (4/82)
Atrial Flutter	2.4% (2/82)
Appendicitis	1.2% (1/82)
Atrial Thrombosis	1.2% (1/82)
Cardiac Tamponade	1.2% (1/82)
Cardio Respiratory Arrest	1.2% (1/82)
Gastrointestinal Hemorrhage	1.2% (1/82)
Injection Site Infection	1.2% (1/82)
Meningitis	1.2% (1/82)
Mental Status Changes	1.2% (1/82)
Pericardial Effusion	1.2% (1/82)
Phrenic Nerve Paralysis	1.2% (1/82)
Renal Failure Acute	1.2% (1/82)
Subdural Hematoma	1.2% (1/82)

Table 24. Serious adverse events occurring in experimental subjects, safety population

Serious Adverse Events	Experimental Subjects % (n / n) N=163
Pneumonia	2.5% (4/163)
Atrial Fibrillation	1.2% (2/163)
Deep Vein Thrombosis	1.2% (2/163)
Myocardial Infarction	1.2% (2/163)
Pulmonary Vein Stenosis	1.2% (2/163)
Asthenia	0.6% (1/163)
Asthma	0.6% (1/163)
Atrial Flutter	0.6% (1/163)
Cardiac Tamponade	0.6% (1/163)
Cardiopulmonary Failure	0.6% (1/163)
Escherichia Bacteremia	0.6% (1/163)
Gastrointestinal Hemorrhage	0.6% (1/163)
Ileitis	0.6% (1/163)
Multi Organ Failure	0.6% (1/163)
Pneumonitis	0.6% (1/163)
Pneumothorax	0.6% (1/163)
Pulmonary Embolism	0.6% (1/163)
Pyelonephritis Acute	0.6% (1/163)
Sepsis	0.6% (1/163)
Soft Tissue Hemorrhage	0.6% (1/163)
Subarachnoid Hemorrhage	0.6% (1/163)
Vessel Puncture Site Hematoma	0.6% (1/163)
Wegener S Granulomatosis	0.6% (1/163)

Death summary

No study subject died within 30 days of a cryoablation procedure. There was one death during the 12 month follow-up period. A 68 year old male Experimental Subject died shortly after a witnessed cardiac arrest occurring 10 months after cryoablation. The event was determined to be unrelated to the study devices, ablation procedure or approved anti-arrhythmic drug therapy.

Pulmonary vein stenosis

PV stenosis was defined by the study protocol as a 75% reduction in area which is roughly a 50% decrease in diameter. Assessment for PV dimensions was done at baseline of 6 and 12 months via CT/MRI scans. Seven of 228 (3.1%) cryoablated study subjects (5 ES and 2 Crossover CS) had one or more stenosed pulmonary veins (PVs) detected during study imaging. Two subjects were symptomatic and their pulmonary vein stenosis adverse events were adjudicated as SAEs and CPEs. Intervention was recommended for both subjects; one declined and the other had angioplasty and stenting with symptomatic improvement. Based on a multivariate analysis there are no known contributing factors to the incidence of PV stenosis.

Phrenic nerve injury

Cryoablation was associated with a high incidence of Transient Phrenic Nerve Dysfunction (TPND) occurring during procedures, which resolved by the end of the procedure and were almost always unassociated with subsequent phrenic nerve dysfunction. Phrenic nerve palsy (PNP), new onset hemi-diaphragmatic movement disorder detected by radiologic assessment, was found after 11.2% (29 / 259) of all cryoablation procedures of which 15 (51.7%) were asymptomatic. All but 4 cases resolved by the end of study follow-up, taking a mean of 158.2 days

(range 1 to 407). Three of 4 persistent PNP cases were symptomatic during follow-up, but none were disabling and only 1 persistent PNP subject had symptoms at the 12 Month visit. Based on a multivariate analysis there are no known contributing factors to the incidence of Phrenic Nerve Palsy.

Strokes and TIAs

Strokes occurred in 5 study subjects (4 ES and 1 CS); only one of these was related to a cryoablation procedure or the devices in a Crossover Control Subject. Of these 5 strokes, one was a subarachnoid hemorrhage from an anterior cerebral artery aneurysm, another was characterized as “whites spots in both eyes” and stroke could not be excluded, and one was a small lacunar stroke found incidentally during a work-up of dizziness. All 5 strokes recovered completely by the conclusion of study follow-up.

Esophageal injury

Esophageal ulcerations have been observed in some subjects who undergo cryoablation with the Arctic Front Cryoablation Catheter. As with other forms of left atrial ablation, the physician should consider appropriate medical strategies to minimize the risk of esophageal injury.

One (1) investigational center performed esophagogastroduodenoscopy post-cryoablation procedure on 12 STOP AF subjects. Of the 12 subjects, 3 were discovered to have esophageal ulcerations. All 3 subjects had follow-up esophagogastroduodenoscopy and demonstrated resolution of esophageal ulceration.

Vascular access complications

Other than routine cases of bruise, hematoma and discharge, there were 4 procedures (4 / 259, 1.5%) associated with significant vascular access site adverse events requiring surgical intervention or transfusion: 1 new AV fistula, 1 worsened pre-existing AV fistula, 2 pseudoaneurysms, and one hemorrhage requiring transfusion. One subject had both an AV fistula and a pseudoaneurysm.

5.9 Summary of STOP AF Pivotal Trial adverse events as categorized using MedDRA

There were a total of 1,406 adverse events (AEs) reported in 235 study subjects during the 12 month period of study follow-up. Seventy-six (76) CS experienced 485 AEs and 159 ES experienced 921 AEs. Ten (10) study subjects had no AEs reported, 6-CS and 4-ES.

In total, 69.2% (45/65) of Crossover CS and 75.5% (123/163) of ES experienced at least one **procedure-related AE**. Overall, the most frequently reported procedure-related AEs (higher than 10%) were back pain (35 subjects, 15.4%) and vessel puncture site hematoma (26 subjects, 11.4%). Other fairly common (higher than 5%) procedure-related AEs included pharyngolaryngeal pain (22 subjects,9.6%), cough (21 subjects, 9.2%), nausea (19 subjects, 8.3%), and procedural pain (15 subjects, 6.6%).

A greater proportion of ES (46.0%) experienced at least one device-related AE compared to Crossover CS (23.1%). The most frequently reported device-related AEs (higher than 10%) were in the following System Organ Class (SOC): Injury, Poisoning and Procedural Complications (Control:12.3%; Experimental: 18.4%), Nervous System Disorders (Control:13.8%; Experimental: 16.6%), Respiratory, Thoracic and Mediastinal Disorders (Control: 6.2%; Experimental: 12.3%), and General Disorders and Administration Site conditions (Control: 4.6%; Experimental: 11.0%). Overall, the only device-related AE occurring in greater than 10% of all cryoablated subjects was phrenic nerve paralysis (28subjects, 12.3%). Other common (higher than 5%) device-related AEs included nerve injury (22 subjects, 9.6%), cough (15 subjects, 6.6%) and venous injury (14 subjects, 6.1%). The majority of the device-related AEs that were observed occurred in less than 2% of subjects.

5.10 Study conclusion

The STOP AF Pivotal Trial demonstrated that there is a reasonable assurance of safety and effectiveness to support the use of the Arctic Front Cardiac Cryoablation Catheter, the Freezor MAX Cryocatheter, FlexCath Steerable Sheath and the CryoConsole (Gen V) in the treatment of patients with drug resistant paroxysmal atrial fibrillation.

6 Clinical summary update

Study title:	STOP AF PAS: Sustained Treatment of Paroxysmal Atrial Fibrillation Post Approval Study (STOP AF PAS)
Number of centers:	39 centers in the United States and Canada
Number of subjects:	402 enrolled subjects

Study purpose – The purpose of STOP AF PAS was to provide clinical evidence of long-term safety and effectiveness of the Arctic Front Cardiac Cryoablation Catheter System, including the Freezor MAX Cardiac Cryoablation Catheter according to the product labeling.[1]

The Arctic Front Cardiac Cryoablation Catheter is indicated for the treatment of drug refractory recurrent symptomatic paroxysmal atrial fibrillation.

6.1 Study design, study population, study visits, and length of follow-up

STOP AF PAS was a prospective multi-center, non-randomized, single arm, unblinded clinical study designed to provide long-term safety and effectiveness of the Arctic Front Cardiac Cryoablation System. The study was powered to test the primary effectiveness and safety hypotheses (i.e. treatment success > 45% at 36 months and frequency of cryoablation procedures events < 14.8% at 12 months post ablation). The study was conducted at 39 centers (32 in United States and 7 in Canada). Of these 39 centers, 6 centers previously participated in the STOP AF and/or CAP AF trials and 33 centers were new Arctic Front users.

Patients with drug refractory paroxysmal atrial fibrillation were considered for the study based on predefined inclusion and exclusion criteria.

Clinical data were required to be collected at baseline/enrollment, during the index ablation procedure, at the pre-discharge visit, and at any retreatments within the blanking period. The study protocol initially required that subjects be seen after the procedure for follow-up visits at 3, 6, and 12 months and 2, 3, 4, and 5 years, but was later amended to reduce the follow-up period to 3 years.

The STOP AF PAS required rhythm monitoring via:

- 12-lead ECG at the discharge, 3, 6, and 12 month, 2 and 3 year, and unscheduled visits
- 24-hour Holter monitoring at the 6 month visit
- 48-hour Holter monitoring at the 12 month, 2 and 3 year visits

6.2 Study endpoints

6.2.1 Primary Endpoints

6.2.1.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint was the rate of subjects free of chronic treatment failure (CTF) at 36 Months.

Chronic treatment failure was defined as:

- Documented atrial fibrillation lasting longer than 30 seconds (outside 90 day blanking period) or
- Intervention for atrial fibrillation (except for repeat cryoablation during the 90 day blanking period)

Intervention for atrial fibrillation was defined as:

- An invasive procedure intended for the definitive treatment of AF, including any ablation of the PVs or atrial triggers (other than protocol specified ablation), interruption of AV nodal function, procedures to alter left atrial conduction or function such as the Maze procedure, or the

[1] This study also included the next generation cryoballoon Arctic Front Advance Cardiac Cryoablation Catheter. Refer to Section 6.3 for enrollments details.

implantation of an atrial pacemaker or atrial defibrillator; whether approved by relevant regulatory authorities or not for such indications; excluding electrical or pharmacologic cardioversion of arrhythmias and excluding procedures solely directed at the treatment of atrial flutter or atrial tachycardias.

6.2.1.2 Primary Safety Endpoint

The primary safety endpoint was the rate of subjects experiencing one or more Cryoablation Procedure Events (CPE) through 12 months.

A CPE was defined as a device-related or procedure-related serious adverse event (SAE) with onset between the time of the subject's entry into the procedure room for the study-specified cryoablation procedure (Day 0) through the indicated onset intervals as set out in *Table 25*.

Table 25. Cryoablation Procedure Events

Cryoablation Procedure Events (CPE)	Onset Interval
Access site complications requiring:	
• Transfusion of 3 or more units or	Through 7 days
• Surgical intervention or	
• Permanent loss or functional impairment	
Cardiac damage (including MI) except for	Through 7 days
• Pulmonary vein stenosis[a]	Through 12 months
• Atrio-esophogeal fistula	Through 12 months
Embolic complications (including stroke)	Through 7 days
Arrhythmias	Through 7 days
• Persistent phrenic nerve palsy[b]	Through 12 months
Death	Through 7 days

[a] CPE was assessed at the completion of the follow-up visit, as determined by CT/MRI Core Lab.

[b] CPE was assessed at the completion of the follow-up as determined by chest X-ray (insp/exp)

6.2.2 Secondary Endpoints

Secondary objectives did not have pre-defined performance criteria but were included to provide additional detail on the performance of the Arctic Front Cardiac Cryoablation Catheter System.

6.2.2.1 Secondary Effectiveness Endpoint

Evaluate the proportion of subjects free of chronic treatment failure at the 1 and 2 year follow-up visits.

6.2.2.2 Secondary Safety Endpoint

Evaluate the proportion of subjects free of Major Atrial Fibrillation Events (MAFE) at the 1, 2, and 3 year follow-up visits.

A MAFE is defined a serious adverse event (SAE) — which has not been categorized as a CPE — as set out in *Table 26*

Table 26. Major Atrial Fibrillation Events

Major Atrial Fibrillation Events (MAFE)
Cardiovascular deaths
Hospitalizations for (primary reason):
AF recurrence or ablation
Atrial flutter ablation (excluding Type I)
Systemic embolization (not stroke)
Congestive heart failure
Hemorrhagic event (not stroke)
Antiarrhythmic drug: initiation, adjustment or complication
Myocardial infarction (MI)
Stroke

6.2.2.3 Long-term Safety Endpoint

Device and procedure related events, SAEs, unexpected adverse device effects and other safety categories collected through the 3 year follow-up and reported descriptively.

6.2.2.4 Cryoablation

Cryoablation procedure parameters will be summarized.

6.2.2.5 Procedure and Fluoroscopy Time

Total procedure time and total fluoroscopy time will be summarized.

6.2.2.6 Adverse Events

All adverse events will be summarized.

6.3 Total number of enrolled study sites and subjects, subject accountability and follow-up rate

Investigators at 39 sites enrolled a total of 402 study subjects of which 70 (17%) were enrolled from centers that previously participated in the STOP AF and/or CAP AF clinical studies, and 332 (83%) were enrolled from new Arctic Front user centers.

Study populations for analysis were:

- **Enrolled:** any patients who have a signed informed consent.
- **Intent-to-treat (ITT):** enrolled subjects that met all inclusion and no exclusion criteria.
- **Modified intent-to-treat (mITT):** Subjects within the ITT set with an Arctic Front Cardiac Cryoablation Catheter System inserted into the vasculature.
- **Modified ITT-AFA:** Subjects within the mITT set with an Arctic Front Advance catheter inserted into the vasculature.

Three hundred seventy (370) subjects were verified as meeting all inclusion and no exclusion criteria and are therefore considered the intent-to-treat (ITT) cohort under this protocol. Of the 370 ITT subjects, 354 met all eligibility criteria, were treated, and comprise the modified intent-to-treat (mITT) cohort. Of the 354 mITT subjects, 344 were treated with an Artic Front Advance cryoballoon and 10 were treated with an Arctic Front cryoballoon. The 344 mITT subjects treated with the Arctic Front Advance will be referred to as mITT-AFA.

Note: Not a pre-specified analysis population.

Subject accountability is described in *Table 27*.

Table 27. Subject disposition

Subject disposition	
Total Subjects Enrolled	N = 402
All inclusion/exclusion criteria met (ITT)	N = 370
All inclusion/exclusion criteria met and a study device inserted into vasculature (mITT)	N = 354
All inclusion/exclusion criteria met and subjects treated with Arctic Front Advance (mITT-AFA)	N = 344
Study complete (mITT cohort)	N = 303

Study exits for the mITT cohort are described in *Table 28*

Table 28. Study exits (mITT Cohort)

Exit timing	Exit Reason	N (%)
Exit prior to 36 months	Failure to maintain adequate study compliance	2 (0.6%)
	Investigator withdrew subject, other	1 (0.3%)
	Lost to follow-up	11 (3.1%)
	Other	1 (0.3%)
	Subject relocated to another geographic location	10 (2.8%)
	Subject requested withdrawal from the study, other	16 (4.5%)
	Subject withdrew consent	5 (1.4%)
Study completion through 3 years	Study completed	303 (85.6%)
Exit after 36 months	Subject requested withdrawal from the study, other	1 (0.3%)
Death	Death	4 (1.1%)[a]

[a] The Adverse Event Adjudication Committee (AEAC) adjudicated each of these events as not related to the procedure or system.

The number of mITT subjects that completed follow-up visits are listed in *Table 29*.

Table 29. Follow-up visits for mITT subjects

Visit Name	Length of CIP defined protocol window	Expected Visits	Visit Completion
3-month	28 days	354	344 (97.2%)
6-month	28 days	351	342 (97.4%)
12-month	30 days	343	325 (94.8%)
2-year	60 days	327	309 (94.5%)
3-year	30 days	308	298 (96.8%)

6.4 Baseline Characteristics

Baseline Characteristics are described in *Table 30*.

Table 30. Baseline Characteristics

	ITT (n = 370)	mITT (n = 354)
Gender (n,%)		
Male	246 (66.5%)	234 (66.1%)
Female	124 (33.5%)	120 (33.9%)
Age (years)		
Mean ± Standard Deviation	60.5±10.4	60.3± 10.5
Median	61	61
25th percentile – 75th percentile	54.0 – 68.0	54.0 – 68.0
Minimum – Maximum	27.0 – 82.0	27.0 – 82.0
Number of Subjects Reporting (N,%)	370 (100.0%)	354 (100.0%)
Race/Ethnic Origin (n,%)		
Subject/physician chose not to provide information	13 (3.5%)	13 (3.7%)
Not reportable per local laws or regulations	0 (0.0%)	0 (0.0%)
American Indian or Alaska Native	1 (0.3%)	1 (0.3%)
Asian	5 (1.4%)	5 (1.4%)
Black or African American	1 (0.3%)	1 (0.3%)
Hispanic or Latino	5 (1.4%)	4 (1.1%)
Native Hawaiian or Pacific Islander	1 (0.3%)	1 (0.3%)
White or Caucasian	343 (92.7%)	328 (92.7%)
Two or more races	0 (0.0%)	0 (0.0%)
Other race	1 (0.3%)	1 (0.3%)
Coronary Artery Disease	39 (10.5%)	34 (9.6%)
Hypertension	187 (50.5%)	176 (49.7%)
NYHA Functional Classification (N, %)		
No history of heart failure	295 (79.7%)	281 (79.4%)
Class I	53 (14.3%)	52 (14.7%)
Class II	22 (5.9%)	21 (5.9%)
Diabetes	37 (10.0%)	36 (10.2%)
Left Atrial Diameter (mm)		
Mean ± Standard Deviation	39.8 ± 5.7	39.8 ± 5.6
Median	40	40
Minimum – Maximum	23.0 – 60.0	23.0 – 60.0
Number of Subjects Reporting (N,%)	356 (96.2%)	342 (96.6%)
History of Atrial Flutter	102 (27.6%)	99 (28.0%)
Previous cardioversions (past 12 months)	119 (32.2%)	111 (31.4%)
Number of All Failed AADs (mean)[a]	1.3 ± 0.5	1.3 ± 0.5
AF episodes in the two months prior to enrollment (count)		
Mean ± Standard Deviation	18.6 ± 35.3	17.7 ± 33.3
Median	6	6
Minimum – Maximum	0.0 – 300.0	0.0 – 300.0
Number of Subjects Reporting (N,%)	362 (97.8%)	347 (98.0%)

[a] Based on ITT cohort of n=367 and mITT cohort of n=351; 3 subjects were not included in these analyses as the necessary records for specific prior failed AADs were missing. The site indicated all three subjects met the inclusion criterion of failing at least one membrane-active AAD for rhythm control prior to enrollment.

6.5 Repeat cryoballoon ablation during the blanking period

Eight (2.3%) subjects in the mITT cohort underwent repeat cryoballoon procedure within the 90-day blanking period. Of these 8 subjects, 3 were reported as chronic treatment failure (CTF); 5 mITT subjects with a repeat cryoablation procedure within the 90-day blanking period remained CTF free.

6.6 Rhythm monitoring compliance

A total of 2046 visits (1618 scheduled) required ECGs to be performed in mITT subjects, of which 1947 (95.2%) were completed. STOP AF PAS protocol did not require Holter monitoring at 3-month or unscheduled visits; 1274 of the 2046 visits required a Holter with overall compliance at 91.4%.

Table 31. Rhythm monitoring compliance in mITT subjects

Visit Name	Completed Visits	Holter Monitoring Compliance[b,c]	Holter Monitoring Before Scheduled Window[d]	Holter Completed Within or After Scheduled Window	ECG Compliance
3-Month	344	N/A	N/A	N/A	339 (98.5%)
6-Month	342	326 (95.3%)	26 (7.6%)	300 (87.7%)	340 (99.4%)

Table 31. Rhythm monitoring compliance in mITT subjects (continued)

Visit Name	Completed Visits	Holter Monitoring Compliance[b,c]	Holter Monitoring Before Scheduled Window[d]	Holter Completed Within or After Scheduled Window	ECG Compliance
12-Month	325	305 (93.8%)	42 (12.9%)	263 (80.9%)	323 (99.4%)
2-Year	309	276 (89.3%)	12 (3.9%)	264 (85.4%)	307 (99.4%)
3-Year	298	257 (86.2%)	49 (16.4%)	208 (69.8%)	295 (99.0%)
All Scheduled Visits	1618	1164 (91.4%)	129 (10.1%)	1035 (81.2%)	1604 (99.1%)
Unscheduled Visits	428	N/A	N/A	N/A	343 (80.1%)
All Visits	2046 (1274 requiring Holter)[a]	1164 (91.4%)	129 (10.1%)	1035 (81.2%)	1947 (95.2%)

[a] Because Holter monitoring was not required at 3-month and unscheduled follow-ups, mITT subjects completed a total of 1274 visit-required Holter monitors per the protocol. Holter compliance rates are calculated using 1274 visits as a denominator.

[b] Holter monitoring compliance is inclusive of completed monitoring outside of study visit window.

[c] Medtronic staff reviewed deviations for evidence of whether Holter monitoring was done for < 24 hours due to technical difficulties or operator error. Only two such instances were found: once at a 12-month follow-up and once at a 3-year visit. These were not counted as compliant in this table.

[d] Holter monitoring before scheduled window is defined as the start of Holter monitoring occurring prior to visit window opening. 129 Holter monitors were started before visit window. 14 of the 129 (10.9%) started prior to visit window, but the 24 or 48 hour duration overlapped and ended within the visit window. The remaining started and ended prior to the visit window open.

6.7 Results

6.7.1 Safety results

6.7.1.1 Primary Objective (Safety)

Definition: The primary safety objective was to demonstrate safety (through 12 months) of Arctic Front Cardiac Cryoablation Catheter System by assessing the rate of subjects experiencing a Cryoablation Procedure Event (CPE).

8 of the 354 mITT subjects reported a cryoablation procedure event (CPE) through 12 months. CPEs are listed in *Table 32*.

Table 32. Cryoballoon Procedure Event (CPE) details: mITT subjects

MedDRA Preferred Term (n = 354)	Number of Events (Number of subjects with event)
Cerebrovascular accident	1 (1)
Haematoma	1 (1)
Pericardial effusion	2 (2)
Phrenic nerve paralysis	3 (3)
Pulmonary vein stenosis	1 (1)
Sinus node dysfunction	1 (1)
Total	9 (8)[a]

[a] One subject was reported to experience both sinus dysfunction and PNI.

The Kaplan-Meier estimate of rate of CPE at 12 months was 2.3% [95% CI: 1.1% - 4.5%]. Because the upper 95% confidence bound (4.5%) is below the predefined performance criteria (14.8%), the primary safety objective is considered met.

6.7.1.2 Secondary Objective #2 (Safety)

Of the 354 mITT subjects, 77 unique subjects reported a total of 95 Major Atrial Fibrillation Events (MAFEs) through 36 months. MAFEs are listed in *Table 33*.

Table 33. Major Atrial Fibrillation Events

Major Atrial Fibrillation Events (MAFEs):		
MAFE category	MedDRA Preferred term	Number of Events (Number of Subjects with event)
Cardiovascular deaths		0 (0)
Hospitalizations for AF recurrence or ablation	Atrial fibrillation	60 (54)
	Atrial tachycardia	1 (1)
	Sinus node dysfunction	1 (1)
Hospitalizations for atrial flutter ablation	Atrial fibrillation	2 (2)
	Atrial flutter	11 (11)
Hospitalizations for Systemic embolization (not stroke)		0 (0)
Hospitalization for congestive heart failure	Cardiac failure congestive	2 (2)
	Cardiomyopathy	1 (1)
Hospitalization for Hemorrhagic event (not stroke)	Brain stem hemorrhage	1 (1)
	Cerebral hemorrhage	1 (1)
	Hemorrhage intracranial	1 (1)
	Subdural hematoma	1 (1)
Hospitalization for Antiarrhythmic drug: initiation, adjustment or complication	Atrial fibrillation	7 (7)
	Atrial flutter	3 (3)
Myocardial infarction (MI)		2 (2)
Stroke	Cerebrovascular Accident	1 (1)

The Kaplan-Meier estimate of freedom from MAFE at 1, 2, and 3 years are:

- 12 months = 90.3% [95% CI: 86.6% - 92.9%]
- 24 months = 83.2% [95% CI: 78.8% - 86.8%]
- 36 months = 77.8% [95% CI: 72.9% - 81.9%]

6.7.1.3 Secondary Objective #3 (Long-Term Safety)

No unexpected adverse device effects (UADE) were reported. The Kaplan-Meier estimates of freedom from adverse events are:

Device related:

- 12 months = 86.7% [95% CI: 82.3% - 89.6%]
- 24 months = 84.9% [95% CI: 80.3% - 87.9%]
- 36 months = 82.9% [95% CI: 76.5% - 85.8%]

Procedure related:

- 12 months = 67.8% [95% CI: 62.6% - 72.4%]
- 24 months = 66.6% [95% CI: 61.4% - 71.2%]
- 36 months = 65.2% [95% CI: 60.0% - 70.0%]

Serious adverse event:

- 12 months = 76.9% [95% CI: 71.8% - 80.7%]
- 24 months = 66.2% [95% CI: 60.6% - 70.7%]
- 36 months = 59.5% [95% CI: 53.6% - 64.2%]

6.7.2 Effectiveness results

6.7.2.1 Primary Efficacy Objective

The primary effectiveness endpoint was the rate of subjects free of chronic treatment failure (CTF), defined as AF recurrence of at least 30 seconds after the 90-day blanking period through 3 years or intervention for atrial fibrillation (except for repeat cryoablation during the 90-day blanking period), at 36 months.

Of the 354 mITT subjects, 114 reported a CTF; 111 occurred prior to 36 months post index ablation, and 3 occurred after 36 months. The freedom from CTF at 36 months was 66.9% [95% CI: 61.6 - 71.7%]. As the lower 95% confidence bound (61.6%) was above the predefined performance criteria (45%), the primary effectiveness objective was considered met.

Figure 4 displays the Kaplan-Meier curve for freedom from chronic treatment failure for mITT subjects (n=354) through 36 months post procedure. The solid line is the Kaplan-Meier estimate, and the dashed lines are the 95% confidence interval. Kaplan-Meier estimate and 95% confidence interval at 36 months post procedure are reported in *Table 34*.

Figure 4. Freedom from Chronic Treatment Failure in mITT subjects at 36 Months

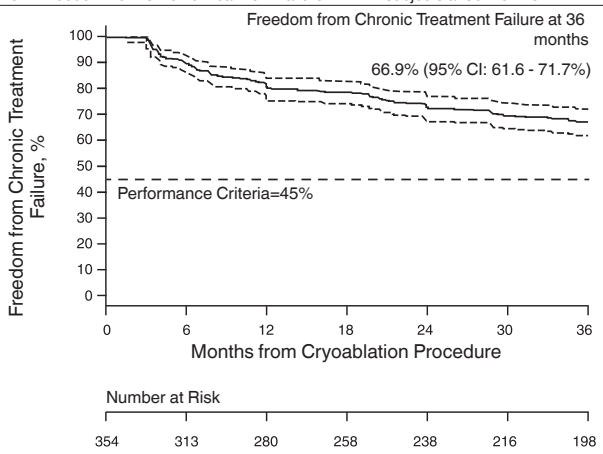


Table 34. Chronic treatment success in mITT subjects at 36 months

Months Since Treatment (n=354)	Kaplan-Meier Rate [95% CI]
36 months	66.9% [95% CI: 61.6 - 71.7%]

Table 35. Primary reason for chronic treatment failure (mITT cohort)

Total number of mITT subjects = 354	Year 1	Year 2	Year 3
Cumulative number of subjects with chronic treatment failure	68	93	111
Documented atrial fibrillation ≥ 30 seconds	58 (85.3%)	79 (84.9%)	96 (86.5%)
Repeat ablation after the 90-day blanking period	9 (13.2%)	13 (14.0%)	14 (12.6%)
RF treatment of atrial fibrillation within 90-day blanking period	1 (1.5%)	1(1.1%)	1 (0.9%)

Table 36. Use of Membrane-Active Atrial Fibrillation Drugs (AFDs) and DC Cardioversion (DCCV)

Total number of mITT subjects	**354**
Total number of successes (no chronic treatment failure)	**243**
Total number of successes who received AFD or DCCV post 90-day blanking period [Count (% of mITT subjects, % of successes)]	**78 (22.0%,32.1%)**
AFD initiated before index procedure and continued beyond 90-day blanking period [Count (% of mITT subjects, % of successes)]	43 (12.1%, 17.7%)
AFD initiated during blanking period and continued beyond 90-day blanking period [Count (% of mITT subjects, % of successes)]	22 (6.2%, 9.1%)
AFD initiated after 90-day blanking period [Count (% of mITT subjects, % of successes)]	12 (3.4%, 4.9%)
AFD initiated 91 – 365 days postprocedure (no DCCV)	9 (2.5%, 3.7%)
AFD initiated 366 – 730 days postprocedure (no DCCV)	1 (0.3%, 0.4%)
AFD initiated > 730 days postprocedure (no DCCV)	2 (0.6%, 0.8%)
AFD initiated before index procedure and continued beyond 90-day blanking period, and DCCV post 90-day blanking period [Count (% of mITT subjects, % of successes)]	1 (0.3%, 0.4%)[a]

[a] Subject was on AFD prior to enrollment, had asymptomatic AF recurrence 21 days into the blanking period, and had a DCCV at day 100.

6.7.2.2 Secondary Objective #1 (Efficacy)

The secondary effectiveness endpoint was to evaluate the proportion of subjects free of chronic treatment failure at the 1 and 2 year follow-up visits. Of the 354 mITT subjects, 68 subjects reported a CTF within the first year and 25 subjects reported a CTF between the first and second year. The freedom from chronic treatment failure (see definition in Section 6.7.2.1) at 1 year was 80.4% [95% CI: 75.9%, 84.2%], and at 2 years was 72.8% [95% CI: 67.7%, 77.2%].

Table 37. Chronic Treatment Success in mITT Subjects at 1 and 2 Years

Years Since Treatment (n=354)	Kaplan-Meier Rate [95% CI]
1 year	80.4% [75.9%, 84.2%]
2 years	72.8% [67.7%, 77.2%]

6.7.2.3 Single Procedure Success

A post hoc analysis was performed to evaluate single procedure success. Single procedure success was defined as freedom from chronic treatment failure (CTF) without repeat cryoablation procedure within the blanking period. Overall, single procedure success was observed in 238 of 354 (67%) mITT subjects at 36 months.

Table 38. Single procedure success

	Freedom from Chronic Treatment Failure		Single Procedure Success Rate	
	Number of Failures	KM Rate (95% CI)	Number of Failures	KM Rate (95% CI)
12 months	68	80.4% (75.9 - 84.2%)	73	79.0% (74.3 – 82.9%)
24 months	93	72.8% (67.7 - 77.2%)	98	71.3% (66.2 – 75.8%)
36 months	111	66.9% (61.6 - 71.7%)	116	65.5% (60.1 – 70.3%)

6.7.2.4 Post Hoc Analysis of Efficacy at 36 Months (mITT-AFA cohort)

Of the 344 mITT- AFA subjects, 104 reported an AF recurrence of at least 30 seconds after the 90-day blanking period through 3 years, and 117 mITT- AFA subjects reported an AF/AFL/AT recurrence of at least 30 seconds after the 90-day blanking period through 3 years. Freedom from AF recurrence and AF/AFL/AT recurrence for mITT- AFA subjects (those subjects treated with Arctic Front Advance) are included in *Table 39*

Table 39. Freedom from AF recurrence and AF/AFL/AT recurrence through 3 years

	Rate of Freedom From AF recurrence [95% CI]	Rate of Freedom From AF/AFL/AT recurrence [95% CI]
36 months	68.1% (62.7 – 72.9%)	64.1% (58.6 – 69.1%)

6.7.2.5 Post Hoc Analysis of Efficacy at 12 and 24 months (mITT-AFA cohort)

Of the 344 mITT-AFA subjects, 62 reported an AF recurrence of at least 30 seconds after the 90-day blanking period through 1 year, and 71 reported an AF/AFL/AT recurrence of at least 30 seconds after the 90-day blanking period through 1 year; 87 reported an AF recurrence of at least 30 seconds after the 90-day blanking period through 2 years, and 97 reported an AF/AFL/AT recurrence of at least 30 seconds after the 90-day blanking period through 2 years. Freedom from AF recurrence and AF/AFL/AT recurrence at 1 year and 2 years for mITT-AFA subjects (those subjects treated with Arctic Front Advance) are included in *Table 40*.

Table 40. Freedom from AF recurrence and AF/AFL/AT recurrence through 1 year and 2 years

	Rate of Freedom From AF recurrence [95% CI]	Rate of Freedom From AF/AFL/AT recurrence [95% CI]
12 months	81.6% (77.1 – 85.4%)	79.0% (74.2 – 82.9%)
24 months	73.8% (68.6 – 78.2%)	70.8% (65.5 – 75.4%)

6.7.3 Additional results

6.7.3.1 Secondary Objective #4 (Cryoablation):

All 354 mITT subjects underwent pulmonary vein ablation with a Cryoballoon. The following data are derived from index procedures only.

- 31 (8.8%) were treated with a 23 mm balloon size
- 314 (88.7%) were treated with a 28 mm balloon size
- 9 (2.5%) were treated with both a 23 mm and 28 mm balloon size

Average number of cryoballoon applications per pulmonary vein was:

- 23 mm: 2.1 ± 1.0
- 28 mm: 2.4 ± 1.2

Average temperature (Celsius) observed during a cryoballoon application was:

- 23 mm: -51.4 ± 14.9
- 28 mm: -45.5 ± 11.7

Average duration of cryoballoon application on a pulmonary vein was:

- 23 mm: 184.2 ± 78.7 seconds
- 28 mm: 200.2 ± 60.8 seconds

25 of 354 (7.1%) mITT subjects had additional focal pulmonary vein ablation

- 4 (1.1%) were treated with a focal cryocatheter
- 21 (5.9%) were treated with a focal radiofrequency (RF) catheter

6.7.3.2 Secondary Objective #5 (Procedure and Fluoroscopy time):

The following data are derived from index procedures only.

Average total procedure time was 232.1 ± 72.6 minutes.

Average total fluoroscopy time was 20.0 ± 12.0 minutes.

6.7.3.3 Secondary Objective #6 (Summary of Adverse Events)

Adverse events occurring during the study were continuously monitored and collected. All adverse events in all enrolled subjects are summarized below. There were no Unanticipated Adverse Device Effects reported in the STOP AF PAS. A total of 957 adverse events have been reported in the study. All 957 events were adjudicated by the Adverse Event Adjudication Committee (AEAC). For adverse event analysis, the AEAC determination of seriousness and relatedness status was used.

A total of six (6) adverse events had an outcome of death. One (1) death occurred in a subject prior to procedure, and five (5) deaths occurred post-procedure: four (4) in mITT subjects, and one (1) in a subject for whom inclusion/exclusion criteria were not met. The AEAC adjudicated each of these events as not related to the procedure or system.

A total of 390 subjects enrolled in this study were considered to be at risk for an adverse event prior to an ablation procedure being performed (all 402 enrolled subjects, excluding 6 subjects rolled over from the CAP-AF/STOP AF studies and 6 subjects with incomplete data from a center that was closed early). Adverse event frequency prior to ablation procedure is reported in *Table 41*. Prior to an ablation procedure, there were 12 subjects (3.1%) who had a total of 15 adverse events.

Table 41. Adverse Events Occurring Prior to Ablation Procedure by MedDRA Preferred Term

	Number of Events (Number, % of Subjects) Total Subjects (N = 390)
Adverse Events	**Events**
Keyterm	
Atrial fibrillation	3 (2, 0.5%)
Acute respiratory failure	1 (1, 0.3%)
Adverse drug reaction	1 (1, 0.3%)
Atrial thrombosis	1 (1, 0.3%)
Diabetic retinal oedema	1 (1, 0.3%)
Diverticulum	1 (1, 0.3%)
Haematuria	1 (1, 0.3%)
Headache	1 (1, 0.3%)
Immune thrombocytopenic purpura	1 (1, 0.3%)
Medication error	1 (1, 0.3%)
Pain in extremity	1 (1, 0.3%)
Sleep apnoea syndrome	1 (1, 0.3%)

Table 41. Adverse Events Occurring Prior to Ablation Procedure by MedDRA Preferred Term (continued)

Syncope	1 (1, 0.3%)
Total Adverse Events	15 (12, 3.1%)

There were 359 subjects who underwent cryoablation for this study; 354 subjects met all inclusion and exclusion criteria (mITT cohort), and 5 subjects were treated but did not meet all inclusion and exclusion criteria. Additionally, 6 subjects underwent cryoablation prior to this protocol (rollover subjects from the STOP AF/CAP AF studies), of which one subject reported an adverse event (hypertension) 1831 days post-ablation. AEs in the 359 treated subjects are summarized below. A summary of the relatedness to the procedure or to any component of the system (including the Balloon cryocatheter, Focal cryocatheter, FlexCath Sheath, CryoConsole, Manual retraction kit, or other) and seriousness are provided in *Table 42*.

Table 42. Relatedness of Adverse Events Occurring During or After Ablation Procedure

Adverse Event Classifications	**Number of Events (Number, % of Subjects) Total Subjects (N = 359)**
Relationship to Procedure	
Not related	741 (270, 75.2%)
Related	195 (126, 35.1%)
Unknown	4 (4, 1.1%)
Missing	0 (0, 0.0%)
Relationship to Device	
Not related	824 (277, 77.2%)
Related	75 (60, 16.7%)
Unknown	41 (35, 9.7%)
Missing	0 (0, 0.0%)
Serious	
Yes	261 (145, 40.4%)
Device related	49 (41, 11.4%)
Procedure related	26 (24, 6.7%)
No	679 (255, 71.0%)
Total Adverse Events	940 (293, 81.6%)

The frequency of serious adverse events is displayed in *Table 43*. A total of 145 of 359 subjects (40.4%) reported a serious adverse event. The most common serious adverse event was atrial fibrillation, reported in 15.6% (56/359) subjects. Of all 957 observed AEs, 940 occurred in the 359 treated subjects (summarized in *Table 42*) on or after the index ablation date; 15 occurred prior to ablation (*Table 41*); one occurred in a CAP-AF rollover subject, and one was a CPE which occurred in a subject with incomplete data from a center that was closed early.

Table 43. Serious Adverse Events Occurring During or After Ablation Procedure by Key Term

		Number of Events (Number, % of Subjects) Total Subjects (N = 359)	
Adverse Events	**Events**	**Device Related**	**Procedure Related**
Keyterm			
Atrial fibrillation	75 (65, 18.1%)	1 (1, 0.3%)	1 (1, 0.3%)
Atrial flutter	20 (20, 5.6%)	14 (14, 3.9%)	12 (12, 3.3%)
Osteoarthritis	9 (8, 2.2%)	0 (0, 0.0%)	0 (0, 0.0%)
Coronary artery disease	5 (3, 0.8%)	0 (0, 0.0%)	0 (0, 0.0%)
Urinary tract infection	5 (5, 1.4%)	3 (3, 0.8%)	0 (0, 0.0%)
Cardiac failure congestive	4 (4, 1.1%)	1 (1, 0.3%)	0 (0, 0.0%)
Meniscus injury	4 (4, 1.1%)	0 (0, 0.0%)	0 (0, 0.0%)
Acute myocardial infarction	3 (3, 0.8%)	1 (1, 0.3%)	0 (0, 0.0%)
Phrenic nerve paralysis	3 (3, 0.8%)	3 (3, 0.8%)	3 (3, 0.8%)
Post procedural haemorrhage	3 (3, 0.8%)	2 (2, 0.6%)	2 (2, 0.6%)
Sinus node dysfunction	3 (3, 0.8%)	1 (1, 0.3%)	1 (1, 0.3%)
Anaemia	2 (2, 0.6%)	0 (0, 0.0%)	0 (0, 0.0%)
Angina pectoris	2 (2, 0.6%)	1 (1, 0.3%)	0 (0, 0.0%)
Angina unstable	2 (2, 0.6%)	0 (0, 0.0%)	0 (0, 0.0%)
Atelectasis	2 (2, 0.6%)	0 (0, 0.0%)	0 (0, 0.0%)
Atrial tachycardia	2 (2, 0.6%)	2 (2, 0.6%)	2 (2, 0.6%)
Bradycardia	2 (2, 0.6%)	1 (1, 0.3%)	1 (1, 0.3%)
Cerebrovascular accident	2 (1, 0.3%)	2 (1, 0.3%)	0 (0, 0.0%)
Chest pain	2 (2, 0.6%)	0 (0, 0.0%)	0 (0, 0.0%)
Cholangitis	2 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Diverticulitis	2 (2, 0.6%)	0 (0, 0.0%)	0 (0, 0.0%)
Dyspnoea	2 (2, 0.6%)	0 (0, 0.0%)	0 (0, 0.0%)
Haematoma	2 (2, 0.6%)	2 (2, 0.6%)	2 (2, 0.6%)
Inguinal hernia	2 (2, 0.6%)	0 (0, 0.0%)	0 (0, 0.0%)
Mental status changes	2 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Pancreatitis	2 (2, 0.6%)	0 (0, 0.0%)	0 (0, 0.0%)
Pericardial effusion	2 (2, 0.6%)	2 (2, 0.6%)	0 (0, 0.0%)
Prostate cancer	2 (2, 0.6%)	0 (0, 0.0%)	0 (0, 0.0%)
Pulmonary vein stenosis	2 (2, 0.6%)	2 (2, 0.6%)	1 (1, 0.3%)
Spinal column stenosis	2 (2, 0.6%)	0 (0, 0.0%)	0 (0, 0.0%)
Squamous cell carcinoma	2 (2, 0.6%)	0 (0, 0.0%)	0 (0, 0.0%)
Accidental death	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Acute kidney injury	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Acute respiratory failure	1 (1, 0.3%)	1 (1, 0.3%)	1 (1, 0.3%)
Allergy to arthropod sting	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Aortic stenosis	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Aortic valve stenosis	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Basal cell carcinoma	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Bladder adenocarcinoma stage unspecified	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Brain stem haemorrhage	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Breast cancer recurrent	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Bronchitis	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Bronchitis viral	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
CHA2DS2-VASc annual stroke risk moderate	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Calculus ureteric	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Cardiac failure	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Cardiomyopathy	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Carpal tunnel syndrome	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Catheter site haemorrhage	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Cauda equina syndrome	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Cellulitis	1 (1, 0.3%)	1 (1, 0.3%)	0 (0, 0.0%)
Cerebral haemorrhage	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Cervical spinal stenosis	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)

Table 43. Serious Adverse Events Occurring During or After Ablation Procedure by Key Term (continued)

Cholecystitis	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Cholecystitis infective	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Cholelithiasis	1 (1, 0.3%)	1 (1, 0.3%)	0 (0, 0.0%)
Chronic obstructive pulmonary disease	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Clostridium difficile colitis	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Clostridium difficile infection	1 (1, 0.3%)	1 (1, 0.3%)	0 (0, 0.0%)
Colitis microscopic	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Colon cancer	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Colostomy closure	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Constipation	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Death	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Diverticular perforation	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Escherichia bacteraemia	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Fall	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Forearm fracture	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Gastric cancer	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Gastrointestinal haemorrhage	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Generalised tonicclonic seizure	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Glaucoma	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Haemoptysis	1 (1, 0.3%)	1 (1, 0.3%)	0 (0, 0.0%)
Haemorrhage intracranial	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Hip fracture	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Hypersensitivity	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Hypotension	1 (1, 0.3%)	1 (1, 0.3%)	0 (0, 0.0%)
Ileus	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Knee arthroplasty	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Lymphadenopathy	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Migraine	1 (1, 0.3%)	1 (1, 0.3%)	0 (0, 0.0%)
Mitral valve calcification	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Multiple sclerosis	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Nephrolithiasis	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Neuralgia	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Nodal rhythm	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Non-cardiac chest pain	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Obesity	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Osteonecrosis	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Osteoporosis	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Pericarditis	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Periprosthetic fracture	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Plasma cell leukaemia	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Pleural effusion	1 (1, 0.3%)	1 (1, 0.3%)	0 (0, 0.0%)
Pneumonia	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Pneumonia bacterial	1 (1, 0.3%)	1 (1, 0.3%)	0 (0, 0.0%)
Post procedural bile leak	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Post procedural pneumonia	1 (1, 0.3%)	1 (1, 0.3%)	0 (0, 0.0%)
Procedural pain	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Psychotic disorder	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Pulmonary mass	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Rectal haemorrhage	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Retinal detachment	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Sepsis	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Small intestinal obstruction	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Spinal compression fracture	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Spinal osteoarthritis	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Squamous cell carcinoma of skin	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Subdural haematoma	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Thyroid cancer	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Toxicity to various agents	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Transient global amnesia	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Trigger finger	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Umbilical hernia	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Urosepsis	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Vascular pseudoaneurysm	1 (1, 0.3%)	1 (1, 0.3%)	0 (0, 0.0%)
Ventricular tachycardia	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Vitreous detachment	1 (1, 0.3%)	0 (0, 0.0%)	0 (0, 0.0%)
Total Adverse Events	**261 (145, 40.4%)**	**49 (41, 11.4%)**	**26 (24, 6.7%)**

6.8 Study strengths and weaknesses

The following points cover the major strengths and weaknesses of the study.

Strengths:

- This large, prospective, multicenter study had sufficient statistical power to test the primary effectiveness and safety hypotheses
- This study provided long term (3-year) effectiveness and safety data on cryoballoon ablation of paroxysmal AF
- Real world perspective (both experienced and new cryoablation users included)
- Independent adjudication of all safety and effectiveness events
- Core Lab for PV stenosis assessments
- Same arrhythmia monitoring methods required for all subjects

Weaknesses:

- Single arm study/ no control group
- The rhythm monitoring employed in the study was limited to periodic ECG and Holter monitoring as well as submission of documented episodes of AF that occurred outside of the protocol-required ECGs and Holters. Therefore, AF episodes that occurred in between the scheduled ECGs/Holters but that were not documented could have been missed. Moreover, the study protocol did not require discontinuation of class I/III AADs after the 3-month blanking period. Instead, the use of class I/III AADs was at the discretion of the investigators. As a result, approximately one-fifth of study subjects were on a class I or III AAD after the 3- month blanking period. All these may have resulted in an overestimation of the effectiveness of cryoballoon ablation in the paroxysmal AF population.

7 Clinical summary update

Study title:	STOP Persistent AF
Number of centers:	22 centers in the United States and Canada
Number of subjects:	169 enrolled and 150 treated subjects in the US and Canada

Study purpose – The purpose of STOP Persistent AF was to demonstrate the safety and effectiveness of the Arctic Front Advance and Freezor MAX Cardiac CryoAblation Catheters for the treatment of symptomatic drug refractory recurrent persistent atrial fibrillation (AF).

7.1 Study design, study population, study visits, and length of follow-up

STOP Persistent AF was a prospective, interventional, multi-center, non-randomized, single arm, unblinded clinical study conducted at 22 centers (19 in United States and 3 in Canada). The first study subject was enrolled in March 2017 and the last subject enrolled in July 2018.

Subjects with drug refractory symptomatic persistent atrial fibrillation of less than 6 months duration were considered for the study based on predefined inclusion and exclusion criteria and underwent pulmonary vein (PV) isolation using the Arctic Front Advance and Freezor MAX Cardiac CryoAblation Catheters. Subjects were followed for 12 months post procedure to assess adverse events and recurrence of atrial tachyarrhythmias.

Clinical data were required to be collected at baseline/enrollment, during the index ablation procedure, at the pre-discharge visit, 6 weeks, 3 months, 6 months and 12 months post ablation, and at any repeat ablations.

The STOP Persistent AF study required rhythm monitoring via:

- 12-lead ECG at baseline, discharge, 3, 6, and 12 months, and unscheduled visits
- 24-hour Holter monitoring at the 6- and 12-month visits
- Trans-telephonic monitoring (TTM) starting at 3 months, weekly and upon symptoms

A core lab was utilized to review tracings from 12-lead ECG, 24-hour Holter and TTM for the adjudication of atrial arrhythmias for the primary effectiveness endpoint evaluation.

An independent Clinical Events Committee (CEC) was utilized to review and adjudicate all device-related and all procedure-related adverse events, as well as all deaths for the primary safety endpoint evaluation.

The study would be considered successful if the pre-defined performance goals for both the primary safety and effectiveness endpoints are met. The performance goal for the primary effectiveness endpoint was set to 40%, and the performance goal for the primary safety endpoint was set to 13%.

7.2 Study endpoints

7.2.1 Primary Endpoints

7.2.1.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint was the proportion of subjects free of treatment failure at 12 months after the PVI ablation procedure.

Treatment success was defined as freedom from treatment failure. Treatment failure was defined as any of the following components:

- Acute procedural failure
- Documented AF/AT/AFL on Holter/TTM/12-lead ECG after the 90-day blanking period
  - Minimum of 30 seconds on Holter/TTM and 10 seconds on 12-lead ECG
- A re-ablation for the treatment of recurrent AF/AT/AFL after the 90-day blanking period
- Class I or III antiarrhythmic drug (AAD) dose increase from the historic maximum ineffective dose (prior to the ablation procedure) or initiation of a new Class I or III AAD after the 90-day blanking period. Note: remaining on the same pre-ablation dose or decreased dose, or re-initiation of a previously failed or not tolerated Class I or III AAD after the 90-day blanking was not considered a failure. Subjects were allowed to remain on Class I or III antiarrhythmic medications at the historic maximum ineffective dose (on prior to the ablation procedure) after the 90-day post-procedure blanking period.
- Ablation using RF in the left atrium

Blanking period was defined as the first 90 days after the index ablation procedure. Recurrences of atrial arrhythmias during the blanking period were not counted in the determination of the first clinical failure for the primary endpoint. Within the blanking period, recurrent arrhythmias could be managed with antiarrhythmic drugs, cardioversion or one cryo re-ablation procedure of the pulmonary veins. Titration of Class I and III antiarrhythmic medications was allowed during the blanking period.

Acute procedural failure was defined as:

- Inability to isolate all accessible targeted pulmonary veins (minimally assessed for entrance block and, where assessable, exit block) during the index procedure; OR
- Left atrial non-PVI ablations including but not limited to, ablation of linear lesions, complex fractionated electrograms or non-PV triggers

7.2.1.2 Primary Safety Endpoint

The primary safety endpoint was the proportion of subjects experiencing one or more primary safety events.

A primary safety event was defined as a serious procedure-related or serious system-related adverse event including the following:

- Transient ischemic attack (within 7 days of ablation procedure)
- Cerebrovascular accident (within 7 days of ablation procedure)
- Major bleeding that requires transfusion (within 7 days of ablation procedure)
- Cardiac perforation, tamponade or pericardial effusion (within 7 days of ablation procedure)
- Pulmonary vein stenosis (>75% reduction within 12-months of ablation procedure)
- Myocardial infarction (within 7 days of ablation procedure)
- Phrenic nerve injury (unresolved at 12-months)
- Atrio-esophageal fistula (within 12-months of ablation procedure)
- Death (within 7 days of ablation procedure)

7.2.2 Secondary Endpoint

The secondary endpoint was the improvement in quality of life between baseline and 12 months as measured by the Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) and SF-12 questionnaires.

7.2.3 Ancillary Endpoint

7.2.3.1 Acute Procedural Success

Acute procedural success was the opposite of acute procedural failure.

7.2.3.2 12-month single procedure success

The same definition as the primary effectiveness endpoint was utilized for 12-month single procedure success, with the additional component that if an ablation occurred during the blanking period, those subjects were set to treatment failure at the date of the blanking period ablation.

7.2.3.3 Procedure measurements

Total procedure time, left atrial dwell time, fluoroscopy time, and application duration were summarized.

7.2.3.4 Treatment success in subjects off Class I and III AADs

This ancillary endpoint compared treatment success in subjects on vs. those off Class I and Class III AADs on day 90 post procedure. The same definition as the primary effectiveness endpoint was utilized for treatment failure.

7.2.3.5 Atrial arrhythmias present and/or treated

All atrial arrhythmias present and/or treated during the cryoablation procedure were summarized.

7.2.3.6 All Adverse Events

All adverse events were summarized.

7.3 Total number of enrolled study sites and subjects, subject accountability and follow-up rate

Investigators at 22 sites in the United States and Canada enrolled a total of 169 subjects of which 150 were treated with an Artic Front Advance cryoballoon. Study populations for analysis were:

- **Enrolled:** Any patients who have a signed informed consent.
- **Modified intent-to-treat (mITT):** Enrolled subjects who maintained informed consent at least until the index cryoablation procedure was finished.

One hundred sixty-nine (169) subjects signed a study informed consent form and were therefore considered the enrolled cohort under this protocol. Of the 169 enrolled subjects, 150 maintained informed consent through the index ablation procedure and thus comprised the modified intent-to-treat (mITT) cohort. All 150 mITT subjects were treated with an Artic Front Advance cryoballoon.

Subject accountability is described in *Table 44*.

Table 44. Subject disposition

Subject disposition	
Total Subjects Enrolled	N = 169
All inclusion/exclusion criteria met and subjects treated with Arctic Front Advance (mITT)	N = 150
Study completed (mITT)	N = 130

Study exits for the mITT cohort are described in *Table 45*

Table 45. Study exits (mITT Cohort)

Number of Subjects Treated (N=150)	
Exit Post-Procedure, Prior to 12 Month Visit	20 (13.3%)
Lost to Follow-Up	6
Subject Requested Withdrawal	6
Other Post-Procedure Exit	8
Completed 12 Months/Study Completed	130 (86.7%)
Death	0 (0.0%)

The number of mITT subjects that completed follow-up visits are listed in *Table 46*.

Table 46. Follow-up visits for mITT subjects

Visit Name	**Length of CIP defined protocol window**	**Expected Visits**	**Visit Completion**
6-week phone call	7 days	150	149 (99.3%)
3-month	30 days	148	144 (97.3%)
6-month	30 days	143	134 (93.7%)
12-month	30 days	140	130 (92.9%)

7.4 Baseline Characteristics

Baseline Characteristics are described in *Table 47*.

Table 47. Baseline Characteristics

	mITT (n = 150)
Sex (N,%)	
Male	105 (70.0%)
Female	45 (30.0%)
Not reported	0 (0.0%)
Age (years)	
Mean ± Standard Deviation	65 ± 9
Median	66
25th percentile – 75th percentile	59 – 72
Minimum – Maximum	38 – 88
Not reported (%)	0 (0%)
Baseline BMI	
Mean ± Standard Deviation	31 ± 6
Median	30
25th percentile – 75th percentile	27 – 35
Minimum – Maximum	17 – 61[a]
Not reported (%)	0 (0%)
Race/Ethnic Origin (N,%)	
White or Caucasian	142 (94.7%)
Subject/physician chose not to provide information	4 (2.7%)
Black	2 (1.3%)
Filipino	1 (0.7%)
Other Asian	1 (0.7%)
Time from First Diagnosis of Persistent AF (years)	
Mean ± Standard Deviation	0.6 ± 1.4
Median	0.2
25th percentile – 75th percentile	0.1 – 0.5
Minimum – Maximum	0.0 – 9.9
Duration of Longest Persistent AF Episode (days)	
Mean ± Standard Deviation	70.9 ± 49.7
Median	60.9
25th percentile – 75th percentile	30.0 – 95.0
Minimum – Maximum	7.0 – 182.6
Number of Prior Cardioversions	
Mean ± Standard Deviation	2.1 ± 2.3
Median	2.0
25th percentile – 75th percentile	1.0 – 3.0
Minimum – Maximum	0.0 – 21.0
Not reported (%)	0 (0.0%)
Cardioversion prior to enrollment	**121 (80.7%)**
Electrical	120 (80.0%)
Pharmacological	15 (10.0%)
Number of Failed Class I/III AADs	
Mean ± Standard Deviation	1.2 ± 0.6
Median	1.0

Table 47. Baseline Characteristics (continued)

	mITT (n = 150)
25th percentile – 75th percentile	1.0 – 1.0
Minimum – Maximum	0.0 – 3.0
Not reported (%)	0 (0.0%)
History of Atrial Flutter (N,%)	
Yes	28 (18.7%)
No	122 (81.3%)
History of Atrial Tachycardia (N,%)	
Yes	3 (2.0%)
No	147 (98.0%)
AF/AT/AFL Symptoms	
Palpitations	98 (65.3%)
Fatigue/Weakness	97 (64.7%)
Dyspnea	95 (63.3%)
Dizziness	46 (30.7%)
Rapid heart beat	33 (22.0%)
Syncope	7 (4.7%)
Other symptoms	51 (34.0%)
None	0 (0.0%)
Left Ventricular Ejection Fraction (%)	
Mean ± Standard Deviation	56 ± 6
Median	55
25th percentile – 75th percentile	54 – 60
Minimum – Maximum	36 – 71
Not reported (%)	0 (0%)
Left Atrial Diameter (cm)	
Mean ± Standard Deviation	4.2 ± 0.6
Median	4.4
25th percentile – 75th percentile	3.8 – 4.7
Minimum – Maximum	2.4 – 5.0
Not reported (%)	3 (2.0%)
Medical History	
Coronary Artery Disease	18 (12.0%)
Myocardial Infarction	7 (4.7%)
Hypertension	93 (62.0%)
Prior Cardiac Valvular Surgery	1 (0.7%)
Diabetes	19 (12.7%)
Congestive Heart Failure	31 (20.7%)
Stroke or TIA	6 (4.0%)
Renal Insufficiency	8 (5.3%)
Sleep Apnea	52 (34.7%)
COPD	10 (6.7%)
CHA_2DS_2-VASc Score	
Mean ± Standard Deviation	2.2 ± 1.4
Median	2
25th percentile – 75th percentile	1 – 3
Minimum – Maximum	0 – 6
≥ 2	101 (67.3%)
Not reported (%)	6 (4.0%)
Baseline Medications	
Beta-blocker	40 (26.7%)
Calcium-channel blocker	32 (21.3%)
Anticoagulant	134 (89.3%)
Aspirin	7 (4.7%)
Class I/III AAD	**91 (60.7%)**
Amiodarone	32 (21.3%)
Dofetilide	4 (2.7%)
Dronedarone	7 (4.7%)
Flecainide	24 (16.0%)
Propafenone	12 (8.0%)
Sotalol	16 (10.7%)
AFEQT Summary Score	
Mean ± Standard Deviation	61.1 ± 20.8
Not reported (%)	2 (1.3%)
SF-12 Physical Component Summary Score	
Mean ± Standard Deviation	43.5 ± 10.5
Not reported (%)	2 (1.3%)
SF-12 Mental Component Summary Score	
Mean ± Standard Deviation	48.5 ± 10.1
Not reported (%)	2 (1.3%)

[a] CIP Versions 1-5 entrance criteria required subjects to have a BMI ≤ 40. CIP Version 6 removed the exclusion criteria of > 40 BMI. Seven (7) subjects were enrolled under CIP v6 with BMI > 40.

7.5 Index Ablation Procedure

Table 48 summarizes the types of ablations performed during the index ablation procedure and the device(s) used. The study protocol required ablation of the cavotricuspid isthmus (CTI) for subjects with a history of typical AFL or inducible CTI-dependent AFL. Additionally, other right atrial ablations were allowed during the index procedure if clinically necessary.

Table 48. Ablations Performed during Index Procedure

Procedural Characteristics	**Subjects with Index Procedures (N = 150)**
Cryoballoon Pulmonary Vein Ablation	**150 (100.0%)**
23 mm balloon size	1 (0.7%)
28 mm balloon size	141 (94.0%)
23 and 28 mm balloon size	8 (5.3%)
Focal Ablation (Freezor MAX) on Pulmonary Vein	**3 (2.0%)**
Focal Ablation (Radiofrequency [RF]) on Pulmonary Vein	**0 (0.0%)**
Cavo-tricuspid Isthmus (CTI) Ablation	**40 (26.7%)**
Focal Cryo	0 (0.0%)
Focal RF	40 (26.7%)
Other Right Atrial Ablations	**3[a] (2.0%)**

[a] Two were atrial tachycardia ablations and one was AVNRT ablation

7.6 Post-ablation AAD therapy

The study protocol recommended discontinuation of Class I and III antiarrhythmic drugs by the end of the 90-day post-procedure blanking period. However, subjects were allowed to remain on Class I or III antiarrhythmic medications at the historic maximum ineffective dose (on prior to the ablation procedure) after the 90-day post-procedure blanking period.

As indicated in *Table 49*, the majority of the 150 treated subjects were on a Class I or III AAD at discharge and about half of the subjects remained on a Class I or III AAD at 3 months post-ablation. More than 30% of the subjects were prescribed a Class I or III AAD at 6 months and 12 months post procedure.

Table 49. Class I/III AAD use at discharge, 3, 6, and 12 months post procedure

Class I/III AAD[a]	N (%) on AAD at Discharge (n = 150)	N (%) on AAD at 3 Months (n=147)	N (%) on AAD at 6 Months (n=142)	N (%) on AAD at 12 Months (n=133)
Number of Subjects on AAD	98 (65.3%)	67 (45.6%)	49 (34.5%)	40 (30.1%)
Amiodarone	33 (22.0%)	18 (12.2%)	13 (9.2%)	12 (9.0%)
Dofetilide	5 (3.3%)	4 (2.7%)	3 (2.1%)	3 (2.3%)
Dronedarone	7 (4.7%)	5 (3.3%)	5 (3.5%)	5 (3.8%)
Flecainide	30 (20.0%)	17 (11.5%)	9 (6.3%)	5 (3.8%)
Propafenone	12 (8.0%)	9 (6.1%)	7 (4.9%)	6 (4.5%)
Sotalol	17 (11.3%)	16 (10.8%)	14 (9.8%)	11 (8.3%)

[a] In this analysis, at months m = 3, 6, and 12, subjects with exit dates prior to month m (or in rare cases, with unknown AAD status) are not included.

7.7 Repeat cryoballoon ablation during the blanking period

The study allowed the following repeat ablations during the 90-day post-procedure blanking period: pulmonary vein isolation ablation using Arctic Front Advance, and ablation in the right atrium.

As shown in *Table 50*, 7 (4.7%) subjects in the mITT cohort underwent a repeat ablation procedure within the 90-day blanking period. Of these 7 subjects, 2 were reported as treatment failures, one due to cryoablation in the left atrium outside of the pulmonary veins and one due to RF ablation of the PV.

Table 50. Details of Repeat Ablations within 90-Day Blanking Period

Subject	Catheter Type	Type of Ablation	Days from Index Procedure	Number of PVs Re-treated	Primary Effectiveness Endpoint Failure?
M100001005	Cryoballoon	PVI	74	4	No
M100001010	Cryoballoon	Left atrial roof line/Left atrial posterior wall	82	0	Yes
M100001011	Cryoballoon	PVI	90	4	No
M100011004	Focal RF	Cavotricuspid Isthmus (CTI line)	42	0	No
M100011007	Focal RF	Cavotricuspid Isthmus (CTI line)	48	0	No
M134170002	Focal RF	Cavotricuspid Isthmus (CTI line)	14	0	No
M200001002	Focal RF	PVI	89	1	Yes

7.8 Rhythm monitoring compliance

Table 51 displays data on compliance to the required 12-lead ECG and 24-Hour Holter during follow-up. A total of 408 completed visits required ECGs to be performed in mITT subjects, of which 408 (100%) were completed. The STOP Persistent AF protocol did not require Holter monitoring at the 3-month or unscheduled visits; 233 of the 264 required Holter were completed, resulting in an overall compliance rate of 88.3%.

Table 51. Rhythm monitoring compliance in mITT subjects

Visit Name	Completed Visits	12-lead ECG Completion	24-Hour Holter Completion
3-Month Follow-Up	144	144 (100.0%)	24-Hour Holter not required
6-Month Follow-Up	134	134 (100.0%)	121 (90.3%)
12-Month Follow-Up	130	130 (100.0%)	112 (86.2%)
Total	408	408 (100.0%)	233 (88.3%)

Figure 5 displays compliance to the required weekly transmissions of trans-telephonic monitoring (TTM). Study subjects were instructed to perform trans-telephonic monitoring (TTM) weekly, beginning one week after the 3-month visit. Subjects were followed for a total of 5225 weeks post 3 months, of which a total of 3772 weekly transmissions were received, resulting in an overall compliance rate of 72.2%, as shown in *Table 52*.

Figure 5. Weekly Trans-Telephonic Monitoring (TTM) Compliance

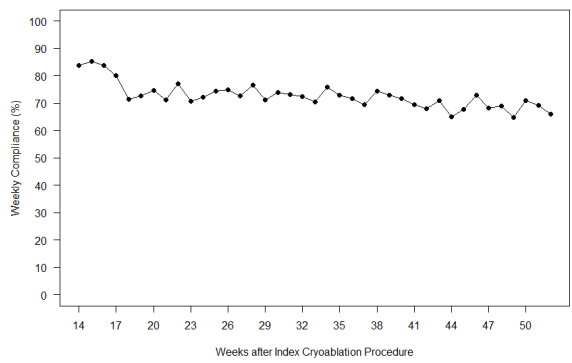


Table 52. Overall TTM Compliance

	Overall TTM Compliance
Number of total weeks of follow up[a],[b]	5225
Number of weeks with reported TTM	3772
Overall TTM compliance	72.2%

[a] TTM transmissions are expected starting 7 days after the 3-month visit. If subject missed 3-month visit, TTM compliance calculations assume transmissions after day 121 (end of 3 month visit window).

[b] This includes eligible weeks between 13- and 52-weeks post ablation, so the maximum number of expected weeks per subject is 40. Week 13 post ablation is not included in the plot, as only subjects receiving TTM equipment at out-of-window early 3-month follow-up visits had expected TTM transmissions in week 13.

In addition to the required weekly TTM transmissions and required study visits, subjects were trained to complete TTM transmissions upon symptoms. In total, an additional 509 TTMs were reported. Also, when a subject attended the clinic for an unscheduled visit, the study required an Unscheduled Visit CRF to be completed which included collection of an ECG. A total of 34 ECG's from unscheduled visits were reported over the duration of the study.

7.9 Results

7.9.1 Safety results

7.9.1.1 Primary Safety Endpoint

Per study protocol, the primary safety analysis included all 150 subjects in whom an Arctic Front Advance Catheter was inserted into their vasculature.

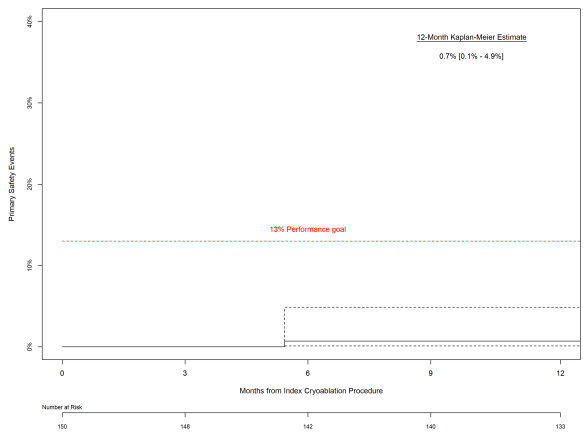
One (1) of the 150 mITT subjects experienced a primary safety event, which was a procedure-related cardiac perforation that occurred during a planned RF repeat ablation procedure . Primary safety events are listed in *Table 53*. There were no primary safety events related to the catheters.

Table 53. Primary Safety Event details: mITT subjects

Primary Safety Event	Number of Subjects with Event (%) Total subjects N = 150
Transient ischemic attack (within 7 days of ablation procedure)	0 (0.0%)
Cerebrovascular accident (within 7 days of ablation procedure)	0 (0.0%)
Major bleeding that requires transfusion (within 7 days of ablation procedure)	0 (0.0%)
Cardiac perforation, tamponade or pericardial effusion (within 7 days of ablation procedure)	1 (0.7%)
Pulmonary vein stenosis (>75% reduction within 12 months of ablation procedure)	0 (0.0%)
Myocardial infarction (within 7 days of ablation procedure)	0 (0.0%)
Phrenic nerve injury (unresolved at 12 months)	0 (0.0%)
Atrio-esophageal fistula (within 12 months of ablation procedure)	0 (0.0%)
Death (within 7 days of ablation procedure)	0 (0.0%)

As depicted in *Figure 6* below, the Kaplan-Meier estimate of rate of primary safety events at 12 months was 0.7% [95% CI: 0.1% - 4.9%]. Because the upper 95% confidence bound (4.9%) is below the predefined performance goal (13%), the primary safety endpoint was met.

Figure 6. Primary Safety at 12 Months



7.9.1.2 Summary of All Adverse Events

Adverse events occurring during the study were continuously monitored and collected. All adverse events in all enrolled subjects are summarized below. There were no Unanticipated Adverse Device Effects or deaths reported in the STOP Persistent AF study. A total of 201 adverse events were reported during the study of which 198 adverse events occurred during or after the index ablation procedure and 3 occurred prior to index ablation procedure (see details in *Table 54*). All events were adjudicated by the Clinical Events Committee (CEC). For adverse event analysis, the CEC determination of seriousness and relatedness status was used.

Table 54. Adverse Events Occurring Prior to Ablation Procedure

Adverse Events	Number of Events (Number of Subjects, % of Subjects) Total subjects: N=169
Electrocardiogram ST segment elevation	1 (1, 0.6%)
Hypotension	1 (1, 0.6%)
Lung neoplasm malignant	1 (1, 0.6%)
Total Adverse Events Prior to Procedure	**3 (3, 1.8%)**

There were 150 subjects who underwent cryoablation in this study. AEs in the 150 treated subjects are summarized below. A summary of the relatedness to the procedure or to any component of the system (including the balloon cryocatheter, focal cryocatheter, FlexCath sheath, CryoConsole, manual retraction kit, or other) and seriousness is provided in *Table 55*.

Table 55. Summary of Adverse Events Reported During or After Index Ablation Procedure

Denominator: mITT Cohort N= 150 **Number of Events (Number of Subjects, % of Subjects)**		
Adverse Event Classifications	**All Adverse Events**	**Serious Adverse Events**
Total Adverse Events	**198 (88, 58.7%)**	**43 (27, 18.0%)**
Relationship to Index CryoAblation Procedure		
Not related	154 (77, 51.3%)	36 (24, 16.0%)
Related	39 (32, 21.3%)	5 (4, 2.7%)
Unknown	0 (0, 0.0%)	0 (0, 0.0%)
Relationship to Repeat CryoAblation Procedure (Number of Repeat CryoAblation procedures = 3)		
Not related	2 (2, 66.7%)	0 (0, 0.0%)
Related	3 (2, 66.7%)	2 (2, 66.7%)
Unknown	0 (0, 0.0%)	0 (0, 0.0%)
Relationship to CryoAblation System		
Not related	172 (82, 54.7%)	40 (25, 16.7%)
Related	25 (22, 14.7%)	3 (3, 2.0%)
- Arctic Front Advance	19 (17, 11.3%)	2 (2, 1.3%)

Table 55. Summary of Adverse Events Reported During or After Index Ablation Procedure (continued)

Denominator: mITT Cohort N= 150		
Number of Events (Number of Subjects, % of Subjects)		
- Freezor MAX	0 (0, 0.0%)	0 (0, 0.0%)
- Achieve Advance Mapping Catheter	0 (0, 0.0%)	0 (0, 0.0%)
- Achieve Mapping Catheter	0 (0, 0.0%)	0 (0, 0.0%)
- FlexCath Advance Sheath	6 (6, 4.0%)	1 (1, 0.7%)
- Manual Retraction Kit	0 (0, 0.0%)	0 (0, 0.0%)
Unknown	1 (1, 0.7%)	0 (0, 0.0%)
Relationship to CardioInsight Mapping System		
Not related	198 (88, 58.7%)	43 (27, 18.0%)
Related	0 (0, 0.0%)	0 (0, 0.0%)
Unknown	0 (0, 0.0%)	0 (0, 0.0%)
Relationship to Other Devices		
Not related	196 (87, 58.0%)	42 (27, 18.0%)
Related	2 (2, 1.3%)	1 (1, 0.7%)
Unknown	0 (0, 0.0%)	0 (0, 0.0%)
Relationship to Other Procedure		
Not related	197 (88, 58.7%)	42 (27, 18.0%)
Related	1[a] (1, 0.7%)	1 (1, 0.7%)
Unknown	0 (0, 0.0%)	0 (0, 0.0%)

[a] The single adverse event related to other procedure was a cardiac perforation that occurred during transseptal puncture. This adverse event was classified by the CEC as related to a repeat RF ablation procedure and was determined to meet the criteria for the primary safety endpoint.

Of the 198 adverse events that occurred during or after the ablation procedure, 43 were classified as serious adverse events (SAEs); 25 adjudicated as related to the cryoablation system, of which 3 were SAEs; and 42 adjudicated as related to a cryoablation procedure, of which 7 were SAEs.

The three (3) cryoablation system-related SAEs were the following:

- Atrial tachycardia (n = 1);
- Pericarditis (n = 1);
- Pseudoaneurysm requiring thrombin injection (n = 1).

The seven (7) cryoablation procedure-related SAEs were the following:

- Atrial tachycardia (n = 1);
- Pericarditis (n = 1);
- Heart failure (n = 1);
- Postoperative ileus (n = 1);
- Respiratory failure (n = 1);
- Urinary tract infection (n = 1);
- Pseudoaneurysm requiring thrombin injection (n = 1).

Table 56 below summarizes all 198 adverse events that occurred during or after the ablation procedure.

Table 56. Relatedness of Adverse Events Occurring During or After Ablation Procedure

Denominator: mITT Cohort (N = 150)						
Number of Events (Number of Subjects, % of Subjects)						
Adverse Events (MedDRA Preferred Term)	**Total Events**	**Serious Adverse Events**	**Cryoablation System Related**	**Serious Cryoablation System Related**	**Cryoablation Procedure Related**	**Serious Cryoablation Procedure Related**
Total	**198 (88, 58.7%)**	**43 (27, 18.0%)**	**25 (22, 14.7%)**	**3 (3, 2.0%)**	**42 (34, 22.7%)**	**7 (6, 4.0%)**
Atrial fibrillation	70 (46, 30.7%)	9 (8, 5.3%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Atrial flutter	24 (20, 13.3%)	(0, 0.0%)	5 (5, 3.3%)	(0, 0.0%)	5 (5, 3.3%)	0 (0, 0.0%)
Chest discomfort	8 (7, 4.7%)	0 (0, 0.0%)	5 (5, 3.3%)	0 (0, 0.0%)	6 (6, 4.0%)	0 (0, 0.0%)
Hypertension	6 (6, 4.0%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Dyspnoea	4 (4, 2.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Palpitations	4 (4, 2.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Hypotension	3 (3, 2.0%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)	2 (2, 1.3%)	0 (0, 0.0%)
Oropharyngeal pain	3 (3, 2.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	3 (3, 2.0%)	0 (0, 0.0%)
Phrenic nerve paralysis	3 (3, 2.0%)[a]	0 (0, 0.0%)	3 (3, 2.0%)	0 (0, 0.0%)	3 (3, 2.0%)	0 (0, 0.0%)
Anaemia	2 (2, 1.3%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Atrial tachycardia	2 (2, 1.3%)	1 (1, 0.7%)	1 (1, 0.7%)	1 (1, 0.7%)	1 (1, 0.7%)	1 (1, 0.7%)
Cardiac failure	2 (2, 1.3%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Cardiac failure congestive	2 (2, 1.3%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Cough	2 (2, 1.3%)	0 (0, 0.0%)	2 (2, 1.3%)	0 (0, 0.0%)	2 (2, 1.3%)	0 (0, 0.0%)
Non-cardiac chest pain	2 (2, 1.3%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Pericarditis	2 (2, 1.3%)	1 (1, 0.7%)	2 (2, 1.3%)	1 (1, 0.7%)	2 (2, 1.3%)	1 (1, 0.7%)
Pneumonia	2 (2, 1.3%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)
Vascular access site haematoma	2 (2, 1.3%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)	2 (2, 1.3%)	0 (0, 0.0%)
Ventricular tachycardia	2 (2, 1.3%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Acute kidney injury	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Acute left ventricular failure	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Acute myocardial infarction	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Angina pectoris	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Aortic perforation	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Arrhythmia supraventricular	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Asthma	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)

Table 56. Relatedness of Adverse Events Occurring During or After Ablation Procedure (continued)

Denominator: mITT Cohort (N = 150) Number of Events (Number of Subjects, % of Subjects)						
Atrioventricular block first degree	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Bacterial sepsis	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Breast cancer	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Bronchitis	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Cardiac failure acute	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	1 (1, 0.7%)	1 (1, 0.7%)
Chest pain	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Cholecystitis chronic	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Conjunctivitis viral	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Coronary artery disease	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Crohn's disease	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Diverticulitis	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Electro-cardiogram QT prolonged	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Epistaxis	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Fluid retention	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Gastro-esophageal reflux disease	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Haemoptysis	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)
Heart rate irregular	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Hemiparesis	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Hyponatraemia	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Incision site haemorrhage	1 (1, 0.7%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)
Labyrinthitis	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Musculoskeletal discomfort	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)
Neck mass	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Odynophagia	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Osteoarthritis	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Pneumothorax	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Postoperative hypotension	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)
Postoperative ileus	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	1 (1, 0.7%)	1 (1, 0.7%)
Procedural hypertension	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)
Puncture site pain	1 (1, 0.7%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)
Respiratory failure	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	1 (1, 0.7%)	1 (1, 0.7%)
Sinus bradycardia	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Sinus tachycardia	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Squamous cell carcinoma of the tongue	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Supraventricular extrasystoles	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Supraventricular tachycardia	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Systolic hypertension	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Transient ischaemic attack	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Ureteric injury	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Urinary tract infection	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	1 (1, 0.7%)	1 (1, 0.7%)
Vaginal haemorrhage	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)
Vascular access site haemorrhage	1 (1, 0.7%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)
Vascular access site pain	1 (1, 0.7%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)	1 (1, 0.7%)	0 (0, 0.0%)
Vascular pseudoaneurysm	1 (1, 0.7%)	1 (1, 0.7%)	1 (1, 0.7%)	1 (1, 0.7%)	1 (1, 0.7%)	1 (1, 0.7%)
Ventricular extrasystoles	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)
Vomiting	1 (1, 0.7%)	1 (1, 0.7%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)	0 (0, 0.0%)

[a] Three (3) phrenic nerve injuries were reported. Two of these resolved prior to discharge from the index ablation. The third resolved after 6 months but prior to the subject's exit from the study.

7.9.1.3 Phrenic Nerve Injury

Phrenic nerve injury resulting in diaphragmatic paralysis occurred in three (3) of 150 subjects (2%) who underwent a cryoballoon ablation procedure. None of the 3 occurrences of diaphragmatic paralysis was classified by the CEC as a SAE. Two of these occurrences resolved prior to discharge from the index ablation. The third persisted for at least 6 months and its recovery was not confirmed on chest x-ray until 15 months post ablation prior to subject's exit from the study. Since this occurrence of diaphragmatic paralysis was not classified as a SAE, the adverse event did not count towards the primary safety endpoint.

7.9.2 Effectiveness results

7.9.2.1 Primary Effectiveness Endpoint

Per study protocol, the primary effectiveness analysis was based on primary effectiveness success using the mITT cohort as the primary analysis population.

Of the 150 mITT subjects, 69 reported at least one primary effectiveness failure through 12 months of follow-up. The distribution of first primary effectiveness failure events observed in the 69 subjects are as follows:

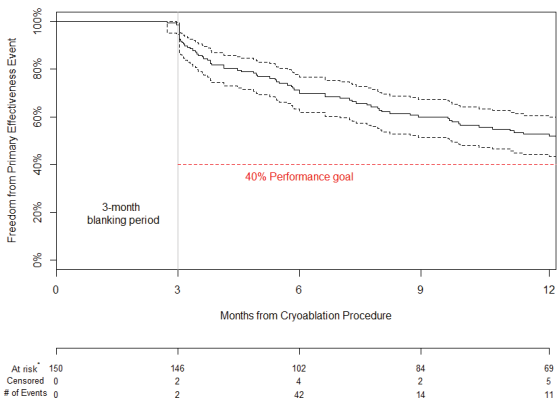
- 0 with acute procedure failures
- 2 with additional interventions in the left atrium within the 90-day blanking period

- 57 with AF/AT/AFL post the blanking period
  - 44 atrial fibrillation (AF)
  - 9 atrial flutter (AFL)
  - 1 atrial fibrillation and atrial flutter
  - 3 atrial tachycardia (AT)
- 10 AAD dose higher than pre-ablation maximum

The rate of freedom from primary effectiveness failure at 12 months was estimated to be 52.1% [95% CI: 43.6 - 59.9%] using the Kaplan-Meier method.

Figure 7 displays the Kaplan-Meier curve for freedom from primary effectiveness failure for mITT subjects (n=150) through 12 months post procedure. The solid line is the Kaplan-Meier estimate, and the dashed lines are the 95% confidence interval. Because the lower bound of 95% confidence interval was greater than the predefined performance goal of 40%, the primary effectiveness endpoint was met.

Figure 7. Freedom from Primary Effectiveness Failure at 12 Months



* The number at risk, number censored, and number of events are included per Kaplan-Meier analysis methods: at risk equals the number of patients at risk up to months 3, 6, 9, and 12; number censored equals the number of patients censored up to months 3, 6, 9, and 12; number of events equals the number of events through the end of the intervals.

Class I/III AAD use in subjects without a primary effectiveness failure event

Data on Class I and III AAD use was collected at each follow-up visit. The study allowed subjects to be remained on a Class I or III AAD at the historic maximum ineffective dose after the blanking period. Per study protocol, such subjects were not classified as primary effectiveness failures for taking a Class I or III AAD during the 9-month effectiveness evaluation period (days 91-365 post procedure).

Among the 150 mITT subjects, 69 were classified as primary effectiveness failures and 81 had not experienced a primary effectiveness failure event. As indicated in *Table 57*, approximately 40% of the subjects without a primary effectiveness failure event remained on a Class I or III AAD at 3 months post procedure. The proportion of the subjects without a primary effectiveness failure event prescribed a previously ineffective Class I or III AAD decreased during the course of 9-month effectiveness evaluation period to approximately 24% at 12 months post procedure.

Table 57. Class I/III AAD use in subjects without a primary effectiveness failure event

	Subjects without a Primary Effectiveness Failure Event (n=81)				
Class I and III AADs[a]	**N (%) on AAD at Baseline (n = 81)**	**N (%) on AAD at Discharge[b] (n = 80)**	**N (%) on AAD at 3 Months[c] (n = 78)**	**N (%) on AAD at 6 Months (n = 74)**	**N (%) on AAD at 12 Months (n = 67)**
Number of Subjects on AAD[d]	47 (58.0%)	50 (62.5%)	30 (38.5%)	21 (28.4%)	16 (23.9%)
Amiodarone	18 (22.2%)	18 (22.5%)	9 (11.5%)	6 (8.1%)	5 (7.5%)
Dofetilide	3 (3.7%)	3 (3.7%)	1 (1.3%)	0	0
Dronedarone	4 (4.9%)	4 (4.9%)	2 (2.5%)	2 (2.7%)	2 (3.0%)
Flecainide	15 (18.5%)	18 (22.2%)	7 (8.9%)	3 (4.0%)	1 (1.5%)
Propafenone	6 (7.4%)	6 (7.4%)	6 (7.6%)	6 (8.0%)	4 (6.0%)
Sotalol	5 (6.2%)	6 (7.4%)	6 (7.6%)	5 (6.7%)	5 (7.5%)

[a] In this analysis, at months m = 3, 6, and 12, subjects with exit dates prior to month m (or in rare cases, with unknown AAD status) are not included.

[b] One subject had no date specified for the discontinuation of amiodarone at a dose less than the pre-ablation maximum; therefore, the status at hospital discharge could not be determined.

[c] Two subjects exited the study during the blanking period, and one subject had no date specified for the discontinuation of amiodarone at a dose less than the pre-ablation maximum; therefore, the status at day 90 for these subjects could not be determined.

[d] Medications and medication changes were captured on a Medication Log CRF. Centers were instructed to update a Medication Log with prescription changes. For analysis, the time at 3 months was defined as day 90, similarly 6 months and 12 months were defined as day 180 and day 365. Prescription data are through study exit.

7.9.2.2 Acute Procedural Success

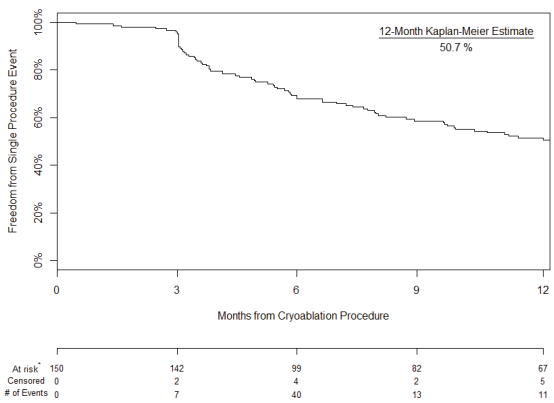
An analysis was performed to evaluate acute procedural success for the mITT cohort.

All 150 mITT subjects experienced acute procedural success (100%) with all pulmonary veins isolated using the study devices at index ablation. A Freezor MAX CryoAblation Catheter was utilized for 4 (0.7%) of 588 pulmonary veins in 3 (2%) of 150 mITT subjects to complete PV isolation.

7.9.2.3 12-month Single Procedural Success

Seven (7) subjects had a repeat ablation within the 90-day blanking period. When these repeat ablations were counted as effectiveness failures, the single procedure success rate was estimated to be 50.7% based on the Kaplan-Meier curve shown in *Figure 8* below.

Figure 8. Single Procedure Freedom from Primary Effectiveness Failure at 12 Months



* The number at risk, number censored, and number of events are included per Kaplan-Meier analysis methods: at risk equals the number of patients at risk up to months 3, 6, 9, and 12; number censored equals the number of patients censored up to months 3, 6, 9, and 12; number of events equals the number of events through the end of the intervals.

7.9.2.4 Treatment Success in subjects off Class I and III AADs

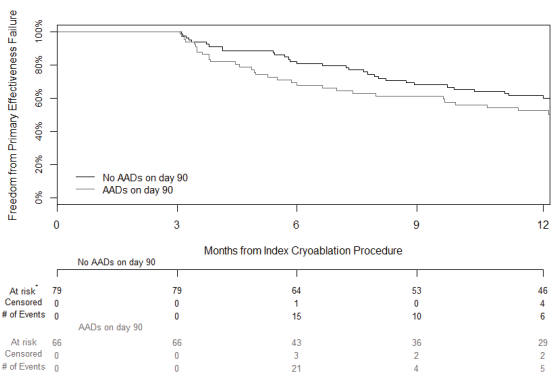
This endpoint compared treatment success in subjects on vs. those off Class I and Class III AADs on day 90 post procedure.

Of the 150 mITT subjects, 145 were included in the analysis. Five (5) subjects were not included due to:

- Study exit prior to 90 days (n = 2);
- primary effectiveness failure prior to day 90 (n =2);
- unknown Class I/III AAD use status on day 90 post procedure (n = 1).

Figure 9 and *Table 58* display the results of primary effectiveness by Class I/III AAD use on day 90 post procedure. Of the 145 subjects included in the analysis, 79 were not prescribed a Class I or III AAD, and 66 were prescribed a Class I or III AAD on day 90. As shown in *Table 58*, the primary effectiveness success rate in subjects who were taking a Class I or III AAD on day 90 post-index ablation was approximately 10% lower than that in those who were not.

Figure 9. Freedom from Primary Effectiveness Failure at 12 Months by Class I/III AAD use on day 90 Post Procedure



* The number at risk, number censored, and number of events are included per Kaplan-Meier analysis methods: at risk equals the number of patients at risk up to months 3, 6, 9, and 12; number censored equals the number of patients censored up to months 3, 6, 9, and 12; number of events equals the number of events through the end of the intervals.

Table 58. Primary Effectiveness Success at 12 Months by Class I/III AAD use on Day 90 Post Procedure

Subgroup	N	Kaplan-Meier Rate
On AAD on Day 90	66	50.4%
Off AAD on Day 90	79	60.2%

7.9.3 Additional results

7.9.3.1 Secondary endpoint (Improvement in Quality of life)

7.9.3.2 AFEQT score

Of the 150 mITT subjects, 126 subjects fully completed a questionnaire at both baseline and 12-month visit. As shown in *Table 59*, the difference in AFEQT score between baseline and 12 months was a statistically significant (<.0001). The average improvement in AFEQT score at 12 months post-index procedure was 26.7 [95% CI: 22.7, 30.8].

Table 59. AFEQT Results through 12 Months

N	Baseline	12 Months Visit	Difference (95% CI)	Unadjusted p-value
126	62.4 ± 20.8	89.1 ± 14.3	26.7 (95% CI: 22.7, 30.8)	<.0001

Figure 10 depicts the change in AFEQT score from baseline through 6 and 12 months. This figure includes all data, not just for the subjects with both baseline and 12 months data available. Therefore, the number of patients included for the baseline AFEQT score was slightly different from that in *Table 59*, however the results were consistent with the paired analysis in *Table 59*. The results showed that the AFEQT score improved at 6 months and the improvement persisted at 12 months post ablation.

Figure 10. AFEQT Results by Visit

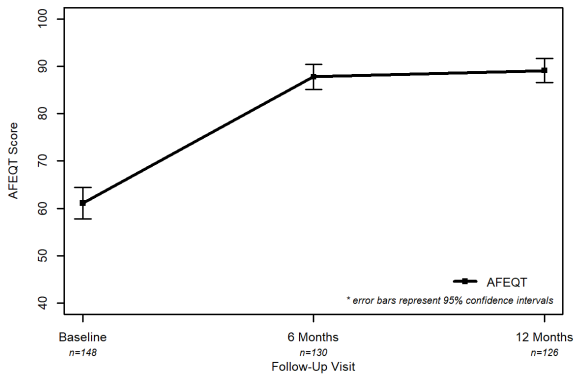


Table 60. AFEQT Results by Visit

Visit	N	Mean ± SD
Baseline	148	61.1 ± 20.8
6 Months Follow-up	130	87.8 ± 15.4
12 Months Follow-up	126	89.1 ± 14.3

7.9.3.3 SF-12 Mental and Physical Scores

Of the 150 mITT subjects, 127 subjects fully completed a SF-12 questionnaire at both baseline and 12-month visit. As shown in *Table 61*, for both the physical and mental components, there was a statistically significant (<.0001) improvement at 12 months post-procedure. The average improvement in SF-12 physical component score was 5.2 [95% CI: 3.7, 6.7]. The average improvement in SF-12 mental component score was 5.1 [95% CI: 3.2, 6.9].

Table 61. SF-12 Results through 12 Months

SF-12 Component	N	Baseline	12 Months Visit	Difference (95% CI)	p-value
SF-12 Physical Component	127	44.0 ± 9.5	49.1 ± 8.3	5.2 (3.7 - 6.7)	<.0001
SF-12 Mental Component	127	49.1 ± 10.1	54.2 ± 7.7	5.1 (3.2 - 6.9)	<.0001

Figure 11 depicts the change in SF-12 scores from baseline through 6 and 12 months. This figure includes all data, not just for the subjects with both baseline and 12 months data available. Thus, there are slight differences in the baseline averages that arise from including the extra subjects. The results showed that both scores increased at 6 months and the improvements persisted at 12 months post ablation.

Figure 11. SF-12 Results through 12 Months

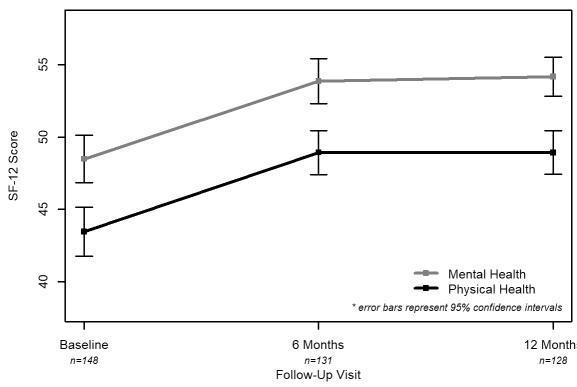


Table 62. SF-12 Summary Scores by Visit

Visit	N	SF-12 Physical Component Mean ± SD	SF-12 Mental Component Mean ± SD
Baseline	148	43.5 ± 10.5	48.5 ± 10.1
6 Months	131	48.9 ± 8.8	53.9 ± 9.0
12 Months	128	48.9 ± 8.6	54.2 ± 7.7

A Hommel multiple testing procedure was utilized to maintain an overall type I error rate of 0.025 for the three hypotheses tested for the secondary endpoints. The three hypotheses tested were change in AFEQT, change in SF-12 mental component, and change in SF-12 physical component. The largest p-value among three tests was < 0.025 (all p-values were < 0.0001). Therefore, according to Hommel multiple testing procedure, all three quality of life endpoints were met.

7.9.3.4 Procedure Measurements

All 150 mITT subjects underwent pulmonary vein ablation with a Cryoballoon. The following data were derived from index procedures only. Summary statistics for procedure times are displayed in *Table 63*.

It is noted that in 8 of 150 index procedures, the last sheath removal occurred in the recovery room at an average of 62.4 minutes (range: 19 – 212 minutes) after the subjects had left the electrophysiology room per physician discretion. Total procedure time and left atrial dwell time calculations ended at the time of last sheath removal.

Table 63. Procedure Measurements

	Subjects with Index Procedures (N = 150)
Total Procedure Time (mins)	
Mean ± Standard Deviation	122 ± 47
Median	113
25th Percentile - 75th Percentile	88 - 146
Minimum - Maximum	48 - 357
Not reported (%)	1 (1%)
Left Atrial Dwell Time (mins)	
Mean ± Standard Deviation	103 ± 42
Median	96

Table 63. Procedure Measurements (continued)

	Subjects with Index Procedures (N = 150)
25th Percentile - 75th Percentile	75 - 117
Minimum - Maximum	43 - 346
Not reported (%)	1 (1%)
Study Device Left Atrial Dwell Time (mins)	
Mean ± Standard Deviation	67 ± 25
Median	65
25th Percentile - 75th Percentile	49 - 81
Minimum - Maximum	16 - 164
Not reported (%)	1 (1%)
Total Fluoroscopy Time (mins)	
Mean ± Standard Deviation	17.0 ± 13.1
Median	14.7
25th Percentile - 75th Percentile	6.8 - 23.9
Minimum - Maximum	0.1 - 65.9
Not reported (%)	3 (2.0%)
Application Duration (mins)	
Mean ± Standard Deviation	24.9 ± 8.0
Median	24.0
25th Percentile - 75th Percentile	19.2 - 28.5
Minimum - Maximum	13.0 - 51.8
Not reported (%)	0 (0.0%)

7.9.3.5 Atrial Arrhythmias Present and/or Treated

Atrial arrhythmias in addition to AF present and/or treated during the index cryoablation procedure are summarized in *Table 64*. The most frequent additional atrial arrhythmia was cavo-tricuspid isthmus (CTI)-dependent atrial flutter.

Table 64. Arrhythmias in addition to AF present and/or treated during the index cryoablation procedure

Arrhythmia	Number of subjects with arrhythmia present N (%) [95% CI]	Number of subjects with arrhythmia treated N (%)
Atrioventricular nodal reentrant tachycardia (AVNRT)	1 (0.7%) [0.0 - 3.7%]	1 (100.0%)
Cavo-tricuspid isthmus (CTI)-dependent Atrial Flutter	40 (26.7%) [19.8 - 34.5%]	40 (100.0%)
Other	4 (2.7%) [0.7 - 6.7%]	2[a] (50.0%)

[a] Both were right atrial tachycardia

7.10 Study conclusions

In conclusion, the results of the STOP Persistent AF study demonstrated that there is a reasonable assurance of safety and effectiveness of the Arctic Front Advance and Freezor MAX Cardiac CryoAblation Catheters when used for the treatment of symptomatic drug refractory recurrent persistent AF of less than 6 months duration.

8 Adverse events

Potential adverse events associated with cardiac catheter cryoablation procedures include, but are not limited to, the following conditions:

- Access site complications (e.g. bruising, ecchymosis)
- Anemia
- Anxiety
- Arrhythmia (e.g. atrial flutter, bradycardia, heart block, tachycardia)
- Back pain
- Bleeding from puncture sites
- Bronchial constriction
- Bronchial fistula
- Bronchitis
- Bruising
- Cardiac tamponade
- Cardiopulmonary arrest
- Cerebral vascular accident
- Chest discomfort/pain/pressure
- Cold feeling
- Coronary artery spasm
- Cough
- Death
- Diarrhea
- Dizziness
- Embolism
- Esophageal damage (including atrio-esophageal fistula)
- Fatigue
- Fever
- Headache
- Hemoptysis
- Hypotension/hypertension
- Infection (e.g. pericarditis, sepsis, urinary)
- Lightheadedness
- Myocardial infarction
- Nausea/vomiting
- Perforation
- Pericardial effusion
- Phrenic nerve injury
- Pleural effusion
- Pneumonia
- Pneumothorax
- Pseudoaneurysm
- Pulmonary edema
- Pulmonary hemorrhage
- Pulmonary vein dissection
- Pulmonary vein stenosis
- Shivering
- Shortness of breath
- Sore throat
- Transient ischemic attack
- Vagal nerve injury (e.g. gastroparesis)
- Vasovagal reaction
- Visual changes (e.g. blurred vision)

9 Instructions for use

9.1 Connecting the Arctic Front Advance Pro Cardiac Cryoablation Catheter

Use standard aseptic technique when removing the product from its sterile barrier and handling the catheter. During connection of the catheter, keep the connections dry at all times. Fluid incursion may lead to system malfunction. To connect the catheter, follow these steps. (For more detailed instructions, see the *CryoConsole Operator's Manual*.)

1. Connect the auto connection box to the CryoConsole.
   Note: The ECG cable is not required for an Arctic Front Advance Pro Cryoballoon procedure, and should not be connected to the auto connection box.
2. Connect the catheter to a sterile electrical umbilical cable and then pass the other end of the cable out of the sterile field and connect it to the auto connection box.
3. Connect the catheter to a sterile coaxial umbilical cable and then pass the other end of the cable out of the sterile field and connect it to the CryoConsole.
4. Enable vacuum on CryoConsole.

9.2 Cryoablation

To use the catheter for a cryoablation procedure, follow these steps. (For more detailed instructions, see the *CryoConsole Operator's Manual*.)

Notes:

- Before introducing the catheter into the patient, test the deflection mechanism on the handle to ensure it is operational.
- Always use the deflection mechanism on the handle to straighten the shaft before insertion or withdrawal of the catheter.

- The Achieve family of mapping catheters is compatible for use with the Medtronic Arctic Front Advance Pro Cryoablation Catheter and may be used to support and position the catheter.

1. Using aseptic technique, create a vascular access with an appropriate introducer. Obtain left atrial transseptal access using a transseptal sheath, its dilator, and needle.
   - Place standard diagnostic pacing catheters.
   - Visualize left atrial anatomy to help select a balloon size. Select balloon size.
   - Selection of balloon size should be based on pulmonary vein (PV) diameter and shape, the surrounding anatomy, and desired position of the balloon outside the tubular portion of the PV. PV diameter ranges are recommended as follows:

     23 mm balloon: 10-21 mm

     28 mm balloon: 16-30 mm
2. Remove the transseptal sheath and dilator, leaving the guide wire positioned preferably in the left superior pulmonary vein (LSPV).
3. Advance the sheath and dilator over the wire into the left atrium.
4. Slowly remove the guide wire and dilator from the sheath.
5. Aspirate and flush the sheath.
6. Obtain a catheter. Connect the y-connector and manifold to the push button Luer.
7. Flush the guide wire lumen, ensuring there are no air bubbles in the guide wire lumen or connections.
8. Load the circular mapping catheter or guide wire into the guide wire lumen.
9. Pull the circular mapping catheter or guide wire back into the balloon catheter until it is just inside the balloon catheter tip.
10. Flush the guide wire lumen again, ensuring there are no air bubbles in the guide wire lumen or connections.
11. Retract the sleeve from the balloon onto the catheter shaft.
12. Submerge and rinse the balloon to remove trapped air bubbles.
13. Advance the sleeve back over the balloon while the balloon is still submerged.
14. Place the sleeve adjacent to the hemostasis valve of the sheath.

    Note: To avoid damaging the valve or introducing air, do not push the sleeve through the valve opening.
15. Insert the catheter into the sheath.

    Notes:
    - To avoid kinking the catheter, grip the catheter shaft at a distance no greater than 30 mm (1.2 in) from the sleeve during insertion.
    - Follow institutional procedures to aspirate and flush the sheath.
16. Advance the balloon until the distal tip of the catheter aligns with the distal tip of the sheath using fluoroscopic guidance or other appropriate visualization techniques.
17. Advance the circular mapping catheter or guide wire to the target pulmonary vein using fluoroscopic guidance or other appropriate visualization techniques.
18. Advance the balloon over the circular mapping catheter or guide wire into the left atrium using fluoroscopic guidance or other appropriate visualization techniques.
19. Inflate the balloon in the left atrium by pressing the Start button on the CryoConsole control panel for 2 s.
20. Position the catheter at the ostium of the target pulmonary vein (PV) and not inside the tubular portion of the PV.
21. Verify the balloon position by injecting a mixture of 50/50 contrast/heparinized saline into the catheter guide wire lumen port or by using other appropriate techniques. Be sure to flush the guide wire lumen with heparinized saline after each contrast injection.

    Notes:
    - To improve balloon position and support, reposition the circular mapping catheter. If a stable balloon position cannot be obtained, exchange the circular mapping catheter for a guide wire.
    - Before exchanging the circular mapping catheter for a guide wire, retract the catheter into the sheath.
    - When using an auto injector for contrast delivery, ensure that the pressure limit does not exceed 500 psig.
    - Follow contrast labeling and institutional procedures regarding the appropriate medical strategies to minimize the risk to the patient associated with using contrast.
22. Perform the cryoablation.

    Notes:
    - During the initial ablation phase, monitor the balloon's position using appropriate visualization techniques. Moisture in the system may cause the inflated balloon to deflate and then re-inflate during the initial transition phases.
    - Set the ablation duration on the CryoConsole screen.
    - Physicians may modify the preset ablation duration based on clinical judgment.
    - The balloon's outer diameter varies from inflation to cryoablation and may cause the balloon to shift.
23. Wait for the cryoablation phase to complete (at the end of the preset duration). The balloon remains inflated and the thawing phase begins.

    Note: At any time, the ablation can be stopped by pressing the Stop Current Action button on the CryoConsole control panel or by pressing the Stop CryoAblation button on the screen.
24. During the thawing phase, observe the temperature indicator on the screen. The balloon deflates automatically when the temperature reaches 20°C.
25. Before moving the balloon, use appropriate techniques to ensure that the catheter is not adhered to tissue.
26. Determine effective ablation of the cardiac tissue by assessing electrical isolation of the pulmonary vein from the left atrium (entrance and exit block) after the cryoablation is complete.

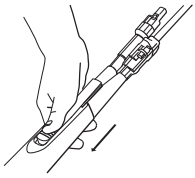
    Note: As needed, perform additional treatments by positioning the balloon differently in the same pulmonary vein.
27. Position the catheter at the ostium of the next target pulmonary vein using the sheath, circular mapping catheter, or guide wire. Return to *Step 17* and continue ablation.
28. To retract the balloon into the sheath, perform the following steps:

    Note: Ensure that the distal tip of the catheter is free to move to its maximum length.
    a. Use the deflection mechanism on the sheath handle to straighten the sheath. Use the deflection mechanism on the catheter handle to straighten the catheter.
    b. Inflate the balloon.
    c. Perform the following two steps simultaneously:

       Advance the blue push button on the catheter handle, as shown in *Figure 12*. This causes the balloon to extend to maximum length and wrap tightly.

       Deflate the balloon by pressing the Stop Current Action button on the CryoConsole control panel, or by selecting the Deflate Balloon option on the screen.
    d. Retract the catheter into the sheath.

Figure 12. Catheter handle



29. Remove the catheter from the patient.
30. After the procedure, follow the instructions to “Shut down the system” in the *CryoConsole Operator’s Manual*. Follow the prompts to close the refrigerant tank and replace the cap on the coaxial port. Confirm these actions when prompted by the CryoConsole.

10 Specifications

Catheter shaft outer diameter	3.5 mm (10.5 Fr; 0.14 in)
Tip length	8 mm (0.31 in)
Tip outer diameter	3.3 mm (9.9 Fr; 0.13 in)
Recommended introducer sheath	compatible Medtronic 12 Fr inner diameter sheath
Inner diameter of guide wire lumen	1.27 mm (0.05 in) nominal
Inflated balloon diameter	AFAPRO23 – 23 mm (0.91 in) AFAPRO28 – 28 mm (1.10 in)
Effective length (with balloon inflated)	95.0 ±2.0 cm (37.40 ±0.80 in)
Number of thermocouples	1
Environmental parameters	
Storage temperature	15°C to 30°C (59°F to 86°F)
Transit temperature	–35°C to 45°C (–31°F to 113°F); up to 85% relative humidity (non-condensing)
Operation	15°C to 30°C (59°F to 86°F) at altitudes less than 2400 m (8000 feet) above sea level

11 Medtronic limited warranty

For complete warranty information, see the accompanying limited warranty document.

12 Service

Medtronic employs highly trained representatives and engineers located throughout the world to serve you and, upon request, to provide training to qualified hospital personnel in the use of Medtronic products. Medtronic also maintains a professional staff to provide technical consultation to product users. For more information, contact your local Medtronic representative, or call or write Medtronic at the appropriate telephone number or address listed on the back cover.

Medtronic

Medtronic, Inc.
710 Medtronic Parkway
Minneapolis, MN 55432
USA
www.medtronic.com
+1 763 514 4000

Medtronic USA, Inc.
Toll-free in the USA (24-hour technical consultation for physicians and medical professionals)
Bradycardia: +1 800 505 4636
Tachycardia: +1 800 723 4636

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